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**WO 03/022273 A1**

(54) Title: METHODS OF TREATING CYTOKINE MEDIATED DISEASES

(57) Abstract: Disclosed are methods of treating acute and chronic inflammation in the lung caused by inhalation of smoke, en-  
dometriosis, Behcet's disease, uveitis, ankylosing spondylitis, pancreatitis, cancer, Lyme disease, sepsis, chronic obstructive pul-  
monary disease, traumatic arthritis, congestive heart failure and restenosis percutaneous transluminal coronary angioplasty, known  
to be cytokine mediated, using aromatic heterocyclic compounds described in WO 00/55139.

## Methods of Treating Cytokine Mediated Diseases

### APPLICATION DATA

5 This application claims benefit to US provisional application serial no. 60/318,958 filed 9/13/2001.

### TECHNICAL FIELD OF THE INVENTION

10 This invention relates to methods of treating acute and chronic inflammation in the lung caused by inhalation of smoke, endometriosis, Behcet's disease, uveitis, ankylosing spondylitis, pancreatitis, cancer, Lyme disease, percutaneous transluminal coronary angioplasty, Alzheimer's disease, traumatic arthritis, sepsis, chronic obstructive  
15 pulmonary disease and congestive heart failure indicated to be cytokine mediated diseases using aromatic heterocyclic compounds disclosed in PCT publication WO 00/55139.

### BACKGROUND OF THE INVENTION

20 In WO 00/55139 there are described aromatic heterocyclic compounds useful in treating certain cytokine mediated diseases. Tumor necrosis factor (TNF) and interleukin-1 (IL-1) are important biological entities collectively referred to as proinflammatory cytokines. These, along with several other related molecules, mediate the inflammatory response  
25 associated with the immunological recognition of infectious agents. The inflammatory response plays an important role in limiting and controlling pathogenic infections.

Elevated levels of proinflammatory cytokines are also associated with a number of diseases of autoimmunity such as toxic shock syndrome, rheumatoid arthritis,  
30 osteoarthritis, diabetes and inflammatory bowel disease (Dinarello, C.A., *et al.*, 1984, *Rev. Infect. Disease* 6:51). In these diseases, chronic elevation of inflammation exacerbates or causes much of the pathophysiology observed. For example, rheumatoid

synovial tissue becomes invaded with inflammatory cells that result in destruction to cartilage and bone (Koch, A.E., *et al.*, 1995, *J. Invest. Med.* 43: 28-38). Studies suggest that inflammatory changes mediated by cytokines may be involved in the pathogenesis of restenosis after percutaneous transluminal coronary angioplasty (PTCA) (Tashiro, H., *et al.*, 2001 Mar, *Coron Artery Dis* 12(2):107-13). An important and accepted therapeutic approach for potential drug intervention in these diseases is the reduction of proinflammatory cytokines such as TNF (also referred to in its secreted cell-free form as TNF $\alpha$ ) and IL-1 $\beta$ . A number of anti-cytokine therapies are currently in clinical trials. Efficacy has been demonstrated with a monoclonal antibody directed against TNF $\alpha$  in a number of autoimmune diseases (Heath, P., "CDP571: An Engineered Human IgG4 Anti-TNF $\alpha$  Antibody" IBC Meeting on Cytokine Antagonists, Philadelphia, PA, April 24-5, 1997). These include the treatment of rheumatoid arthritis, Crohn's disease and ulcerative colitis (Rankin, E.C.C., *et al.*, 1997, *British J. Rheum.* 35: 334-342 and Stack, W.A., *et al.*, 1997, *Lancet* 349: 521-524). The monoclonal antibody is thought to function by binding to both soluble TNF $\alpha$  and to membrane bound TNF.

A soluble TNF $\alpha$  receptor has been engineered that interacts with TNF $\alpha$ . The approach is similar to that described above for the monoclonal antibodies directed against TNF $\alpha$ ; both agents bind to soluble TNF $\alpha$ , thus reducing its concentration. One version of this construct, called Enbrel (Immunex, Seattle, WA) recently demonstrated efficacy in a Phase III clinical trial for the treatment of rheumatoid arthritis (Brower *et al.*, 1997, *Nature Biotechnology* 15: 1240). Another version of the TNF $\alpha$  receptor, Ro 45-2081 (Hoffman-LaRoche Inc., Nutley, NJ) has demonstrated efficacy in various animal models of allergic lung inflammation and acute lung injury. Ro 45-2081 is a recombinant chimeric molecule constructed from the soluble 55 kDa human TNF receptor fused to the hinge region of the heavy chain IgG1 gene and expressed in eukaryotic cells (Renzetti, *et al.*, 1997, *Inflamm. Res.* 46: S143).

IL-1 has been implicated as an immunological effector molecule in a large number of disease processes. IL-1 receptor antagonist (IL-1ra) had been examined in human clinical trials. Efficacy has been demonstrated for the treatment of rheumatoid arthritis (Antril,

Amgen). In a phase III human clinical trial IL-1ra reduced the mortality rate in patients with septic shock syndrome (Dinarello, 1995, *Nutrition* 11, 492). Osteoarthritis is a slow progressive disease characterized by destruction of the articular cartilage. IL-1 is detected in synovial fluid and in the cartilage matrix of osteoarthritic joints. Antagonists of IL-1 have been shown to diminish the degradation of cartilage matrix components in a variety of experimental models of arthritis (Chevalier, 1997, *Biomed Pharmacother.* 51, 58). Nitric oxide (NO) is a mediator of cardiovascular homeostasis, neurotransmission and immune function; recently it has been shown to have important effects in the modulation of bone remodeling. Cytokines such as IL-1 and TNF are potent stimulators of NO production. NO is an important regulatory molecule in bone with effects on cells of the osteoblast and osteoclast lineage (Evans, *et al.*, 1996, *J Bone Miner Res.* 11, 300). The promotion of beta-cell destruction leading to insulin dependent diabetes mellitus shows dependence on IL-1. Some of this damage may be mediated through other effectors such as prostaglandins and thromboxanes. IL-1 can effect this process by controlling the level of both cyclooxygenase II and inducible nitric oxide synthetase expression (McDaniel *et al.*, 1996, *Proc Soc Exp Biol Med.* 211, 24).

Inhibitors of cytokine production are expected to block inducible cyclooxygenase (COX-2) expression. COX-2 expression has been shown to be increased by cytokines and it is believed to be the isoform of cyclooxygenase responsible for inflammation (M.K. O'Banion *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, 1992, 89, 4888.) Accordingly, inhibitors of cytokines such as IL-1 would be expected to exhibit efficacy against those disorders currently treated with COX inhibitors such as the familiar NSAIDs. These disorders include acute and chronic pain as well as symptoms of inflammation and cardiovascular disease.

Elevation of several cytokines have been demonstrated during active inflammatory bowel disease (IBD). A mucosal imbalance of intestinal IL-1 and IL-1ra is present in patients with IBD. Insufficient production of endogenous IL-1ra may contribute to the pathogenesis of IBD (Cominelli, *et al.*, 1996, *Aliment Pharmacol Ther.* 10, 49). Alzheimer disease is characterized by the presence of beta-amyloid protein deposits,



neurofibrillary tangles and cholinergic dysfunction throughout the hippocampal region.

The structural and metabolic damage found in Alzheimer disease is possibly due to a sustained elevation of IL-1 (Holden, *et al.*, 1995, *Med Hypotheses*, 45, 559). A role for IL-1 in the pathogenesis of human immunodeficiency virus (HIV) has been identified.

5 IL-1ra showed a clear relationship to acute inflammatory events as well as to the different disease stages in the pathophysiology of HIV infection (Kreuzer, *et al.*, 1997, *Clin Exp Immunol.* 109, 54). IL-1 and TNF are both involved in periodontal disease. The destructive process associated with periodontal disease may be due to a dysregulation of both IL-1 and TNF (Howells, 1995, *Oral Dis.* 1, 266).

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Proinflammatory cytokines such as TNF $\alpha$  and IL-1 $\beta$  are also important mediators of septic shock and associated cardiopulmonary dysfunction, acute respiratory distress syndrome (ARDS) and multiple organ failure. In a study of patients presenting at a hospital with sepsis, a correlation was found between TNF $\alpha$  and IL-6 levels and septic complications (Terregino *et al.*, 2000, *Ann. Emerg. Med.*, 35, 26). TNF $\alpha$  has also been implicated in cachexia and muscle degradation, associated with HIV infection (Lahdiverta *et al.*, 1988, *Amer. J. Med.*, 85, 289). Obesity is associated with an increase incidence of infection, diabetes and cardiovascular disease. Abnormalities in TNF $\alpha$  expression have been noted for each of the above conditions (Loffreda, *et al.*, 1998, 15 *FASEB J.* 12, 57). It has been proposed that elevated levels of TNF $\alpha$  are involved in other eating related disorders such as anorexia and bulimia nervosa. Pathophysiological parallels are drawn between anorexia nervosa and cancer cachexia (Holden, *et al.*, 1996, *Med Hypotheses* 47, 423). An inhibitor of TNF $\alpha$  production, HU-211, was shown to improve the outcome of closed brain injury in an experimental model (Shohami, *et al.*, 20 1997, *J Neuroimmunol.* 72, 169). Atherosclerosis is known to have an inflammatory component and cytokines such as IL-1 and TNF have been suggested to promote the disease. In an animal model an IL-1 receptor antagonist was shown to inhibit fatty streak formation (Elhage *et al.*, 1998, *Circulation*, 97, 242).

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30 TNF $\alpha$  levels are elevated in airways of patients with chronic obstructive pulmonary disease and it may contribute to the pathogenesis of this disease (M.A. Higham *et al.*,

2000, *Eur. Respiratory J.*, 15, 281). Circulating TNF $\alpha$  may also contribute to weight loss associated with this disease (N. Takabatake *et al.*, 2000, *Amer. J. Resp. & Crit. Care Med.*, 161 (4 Pt 1), 1179). Elevated TNF $\alpha$  levels have also been found to be associated with congestive heart failure and the level has been correlated with severity of the disease  
5 (A.M. Feldman *et al.*, 2000, *J. Amer. College of Cardiology*, 35, 537). In addition, TNF $\alpha$  has been implicated in reperfusion injury in lung (Borjesson *et al.*, 2000, *Amer. J. Physiol.*, 278, L3-12), kidney (Lemay *et al.*, 2000, *Transplantation*, 69, 959), and the nervous system (Mitsui *et al.*, 1999, *Brain Res.*, 844, 192).

10 TNF $\alpha$  is also a potent osteoclastogenic agent and is involved in bone resorption and diseases involving bone resorption (Abu-Amer *et al.*, 2000, *J. Biol. Chem.*, 275, 27307). It has also been found highly expressed in chondrocytes of patients with traumatic arthritis (Melchiorri *et al.*, 2000, *Arthritis and Rheumatism*, 41, 2165). TNF $\alpha$  has also been shown to play a key role in the development of glomerulonephritis (Le Hir *et al.*,  
15 1998, *Laboratory Investigation*, 78, 1625).

The abnormal expression of inducible nitric oxide synthetase (iNOS) has been associated with hypertension in the spontaneously hypertensive rat (Chou *et al.*, 1998, *Hypertension*, 31, 643). IL-1 has a role in the expression of iNOS and therefore may also have a role in  
20 the pathogenesis of hypertension (Singh *et al.*, 1996, *Amer. J. Hypertension*, 9, 867).

IL-1 has also been shown to induce uveitis in rats which could be inhibited with IL-1 blockers. (Xuan *et al.*, 1998, *J. Ocular Pharmacol. and Ther.*, 14, 31). Cytokines including IL-1, TNF and GM-CSF have been shown to stimulate proliferation of acute  
25 myelogenous leukemia blasts (Bruserud, 1996, *Leukemia Res.* 20, 65). IL-1 was shown to be essential for the development of both irritant and allergic contact dermatitis. Epicutaneous sensitization can be prevented by the administration of an anti- IL-1 monoclonal antibody before epicutaneous application of an allergen (Muller, *et al.*, 1996, *Am J Contact Dermat.* 7, 177). Data obtained from IL-1 knock out mice indicates the  
30 critical involvement in fever for this cytokine (Kluger *et al.*, 1998, *Clin Exp Pharmacol Physiol.* 25, 141). A variety of cytokines including TNF, IL-1, IL-6 and IL-8 initiate the

acute-phase reaction which is stereotyped in fever, malaise, myalgia, headaches, cellular hypermetabolism and multiple endocrine and enzyme responses (Beisel, 1995, *Am J Clin Nutr.* 62, 813). The production of these inflammatory cytokines rapidly follows trauma or pathogenic organism invasion.

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Other proinflammatory cytokines have been correlated with a variety of disease states. IL-8 correlates with influx of neutrophils into sites of inflammation or injury. Blocking antibodies against IL-8 have demonstrated a role for IL-8 in the neutrophil associated tissue injury in acute inflammation (Harada *et al.*, 1996, *Molecular Medicine Today* 2, 482). Therefore, an inhibitor of IL-8 production may be useful in the treatment of diseases mediated predominantly by neutrophils such as stroke and myocardial infarction, alone or following thrombolytic therapy, thermal injury, adult respiratory distress syndrome (ARDS), multiple organ injury secondary to trauma, acute glomerulonephritis, dermatoses with acute inflammatory components, acute purulent meningitis or other central nervous system disorders, hemodialysis, leukopheresis, granulocyte transfusion associated syndromes, and necrotizing enterocolitis.

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Rhinovirus triggers the production of various proinflammatory cytokines, predominantly IL-8, which results in symptomatic illnesses such as acute rhinitis (Winther *et al.*, 1998, *Am J Rhinol.* 12, 17).

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Other diseases that are effected by IL-8 include myocardial ischemia and reperfusion, inflammatory bowel disease and many others.

The proinflammatory cytokine IL-6 has been implicated with the acute phase response.

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IL-6 is a growth factor in a number in oncological diseases including multiple myeloma and related plasma cell dyscrasias (Treon, *et al.*, 1998, *Current Opinion in Hematology* 5: 42). It has also been shown to be an important mediator of inflammation within the central nervous system. Elevated levels of IL-6 are found in several neurological disorders including AIDS dementia complex, Alzheimer's disease, multiple sclerosis, systemic lupus erythematosus, CNS trauma and viral and bacterial meningitis (Gruol, *et al.*, 1997, *Molecular Neurobiology* 15: 307). IL-6 also plays a significant role in

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osteoporosis. In murine models it has been shown to effect bone resorption and to induce osteoclast activity (Ershler *et al.*, 1997, *Development and Comparative Immunol.* 21: 487). Marked cytokine differences, such as IL-6 levels, exist in vivo between osteoclasts of normal bone and bone from patients with Paget's disease (Mills, *et al.*, 1997, *Calcif Tissue Int.* 61, 16). A number of cytokines have been shown to be involved in cancer cachexia. The severity of key parameters of cachexia can be reduced by treatment with anti IL-6 antibodies or with IL-6 receptor antagonists (Strassmann, *et al.*, 1995, *Cytokines Mol Ther.* 1, 107). Several infectious diseases, such as influenza, indicate IL-6 and IFN alpha as key factors in both symptom formation and in host defense (Hayden, *et al.*, 1998, *J Clin Invest.* 101, 643). Overexpression of IL-6 has been implicated in the pathology of a number of diseases including multiple myeloma, rheumatoid arthritis, Castleman's disease, psoriasis and post-menopausal osteoporosis (Simpson, *et al.*, 1997, *Protein Sci.* 6, 929). Compounds that interfered with the production of cytokines including IL-6, and TNF were effective in blocking a passive cutaneous anaphylaxis in mice (Scholz *et al.*, 1998, *J. Med. Chem.*, 41, 1050).

GM-CSF is another proinflammatory cytokine with relevance to a number of therapeutic diseases. It influences not only proliferation and differentiation of stem cells but also regulates several other cells involved in acute and chronic inflammation. Treatment with GM-CSF has been attempted in a number of disease states including burn-wound healing, skin-graft resolution as well as cytostatic and radiotherapy induced mucositis (Masucci, 1996, *Medical Oncology* 13: 149). GM-CSF also appears to play a role in the replication of human immunodeficiency virus (HIV) in cells of macrophage lineage with relevance to AIDS therapy (Crowe *et al.*, 1997, *Journal of Leukocyte Biology* 62, 41). Bronchial asthma is characterised by an inflammatory process in lungs. Involved cytokines include GM-CSF amongst others (Lee, 1998, *J R Coll Physicians Lond* 32, 56).

Interferon  $\gamma$  (IFN  $\gamma$ ) has been implicated in a number of diseases. It has been associated with increased collagen deposition that is a central histopathological feature of graft-versus-host disease (Parkman, 1998, *Curr Opin Hematol.* 5, 22). Following kidney transplantation, a patient was diagnosed with acute myelogenous leukemia.

Retrospective analysis of peripheral blood cytokines revealed elevated levels of GM-CSF and IFN  $\gamma$ . These elevated levels coincided with a rise in peripheral blood white cell count (Burke, *et al.*, 1995, *Leuk Lymphoma*. 19, 173). The development of insulin-dependent diabetes (Type 1) can be correlated with the accumulation in pancreatic islet cells of T-cells producing IFN  $\gamma$  (Ablumunits, *et al.*, 1998, *J Autoimmun.* 11, 73). IFN  $\gamma$  along with TNF, IL-2 and IL-6 lead to the activation of most peripheral T-cells prior to the development of lesions in the central nervous system for diseases such as multiple sclerosis (MS) and AIDS dementia complex (Martino *et al.*, 1998, *Ann Neurol.* 43, 340). Atherosclerotic lesions result in arterial disease that can lead to cardiac and cerebral infarction. Many activated immune cells are present in these lesions, mainly T-cells and macrophages. These cells produce large amounts of proinflammatory cytokines such as TNF, IL-1 and IFN  $\gamma$ . These cytokines are thought to be involved in promoting apoptosis or programmed cell death of the surrounding vascular smooth muscle cells resulting in the atherosclerotic lesions (Geng, 1997, *Heart Vessels Suppl* 12, 76). Allergic subjects produce mRNA specific for IFN  $\gamma$  following challenge with *Vespula* venom (Bonay, *et al.*, 1997, *Clin Exp Immunol.* 109, 342). The expression of a number of cytokines, including IFN  $\gamma$  has been shown to increase following a delayed type hypersensitivity reaction thus indicating a role for IFN  $\gamma$  in atopic dermatitis (Szepietowski, *et al.*, 1997, *Br J Dermatol.* 137, 195). Histopathologic and immunohistologic studies were performed in cases of fatal cerebral malaria. Evidence for elevated IFN  $\gamma$  amongst other cytokines was observed indicating a role in this disease (Udomsangpetch *et al.*, 1997, *Am J Trop Med Hyg.* 57, 501). The importance of free radical species in the pathogenesis of various infectious diseases has been established. The nitric oxide synthesis pathway is activated in response to infection with certain viruses via the induction of proinflammatory cytokines such as IFN  $\gamma$  (Akaike, *et al.*, 1998, *Proc Soc Exp Biol Med.* 217, 64). Patients, chronically infected with hepatitis B virus (HBV) can develop cirrhosis and hepatocellular carcinoma. Viral gene expression and replication in HBV transgenic mice can be suppressed by a post-transcriptional mechanism mediated by IFN  $\gamma$ , TNF and IL-2 (Chisari, *et al.*, 1995, *Springer Semin Immunopathol.* 17, 261). IFN  $\gamma$  can selectively inhibit cytokine induced bone resorption. It appears to do this via the intermediacy of nitric oxide (NO) which is an important regulatory molecule in bone

remodeling. NO may be involved as a mediator of bone disease for such diseases as: the rheumatoid arthritis, tumor associated osteolysis and postmenopausal osteoporosis (Evans, *et al.*, 1996, *J Bone Miner Res.* 11, 300). Studies with gene deficient mice have demonstrated that the IL-12 dependent production of IFN  $\gamma$  is critical in the control of  
5 early parasitic growth. Although this process is independent of nitric oxide the control of chronic infection does appear to be NO dependent (Alexander *et al.*, 1997, *Philos Trans R Soc Lond B Biol Sci* 352, 1355). NO is an important vasodilator and convincing evidence exists for its role in cardiovascular shock (Kilbourn, *et al.*, 1997, *Dis Mon.* 43, 277). IFN  $\gamma$  is required for progression of chronic intestinal inflammation in such  
10 diseases as Crohn's disease and inflammatory bowel disease (IBD) presumably through the intermediacy of CD4+ lymphocytes probably of the TH1 phenotype (Sartor 1996, *Aliment Pharmacol Ther.* 10 Suppl 2, 43). An elevated level of serum IgE is associated with various atopic diseases such as bronchial asthma and atopic dermatitis. The level of IFN  $\gamma$  was negatively correlated with serum IgE suggesting a role for IFN  $\gamma$  in atopic  
15 patients (Teramoto *et al.*, 1998, *Clin Exp Allergy* 28, 74).

WO 01/01986 discloses particular compounds alleged to having the ability to inhibit TNF-alpha. The specific inhibitors disclosed are structurally distinct from the novel compounds disclosed in the present application disclosed hereinbelow. Certain  
20 compounds disclosed in WO 01/01986 are indicated to be effective in treating the following diseases: dementia associated with HIV infection, glaucoma, optic-neuropathy, optic neuritis, retinal ischemia, laser induced optic damage, surgery or trauma-induced proliferative vitreoretinopathy, cerebral ischemia, hypoxia-ischemia, hypoglycemia, domoic acid poisoning, anoxia, carbon monoxide or manganese or cyanide poisoning,  
25 Huntington's disease, Alzheimer's disease, Parkinson's disease, meningitis, multiple sclerosis and other demyelinating diseases, amyotrophic lateral sclerosis, head and spinal cord trauma, seizures, convulsions, olivopontocerebellar atrophy, neuropathic pain syndromes, diabetic neuropathy, HIV-related neuropathy, MERRF and MELAS syndromes, Leber's disease, Wernicke's encephalopathy, Rett syndrome,  
30 homocysteinuria, hyperprolinemia, hyperhomocysteinemia, nonketotic hyperglycinemia, hydroxybutyric aminoaciduria, sulfite oxidase deficiency, combined systems disease, lead

encephalopathy, Tourett's syndrome, hepatic encephalopathy, drug addiction, drug tolerance, drug dependency, depression, anxiety and schizophrenia. WO 02/32862 discloses that inhibitors of pro-inflammatory cytokines including TNF $\alpha$  are allegedly useful for treating acute and chronic inflammation in the lung caused by inhalation of smoke such as cigarette smoke. TNF $\alpha$  antagonists are apparently also useful for the treatment of endometriosis, see EP 1022027 A1. Infliximab, in clinical trials for RA, has also been indicated to be useful for treating various inflammatory diseases including Behcet's disease, uveitis and ankylosing spondylitis. Pancreatitis may also be regulated by inflammatory mediator production, see J Surg Res 2000 May 15 90(2)95-101; Shock 1998 Sep. 10(3):160-75. p38MAPkinase pathway plays an role in B.burgdorferi-elicited inflammation and may be useful in treating inflammation induced by the Lyme disease agent. Anguita, J. et. al., *The Journal of Immunology*, 2002,168:6352-6357.

Anti-cytokine drugs may also have therapeutic utility in treating tumor cells. Drug Resistance Updates 4(4):253-267, 2001 Aug. WO 02/38143 discloses the use of p38 inhibitors to enhance the efficacy and safety of genotoxic therapy for treating, for example, aging, cancer and certain types of heart failure.

Compounds which modulate release of one or more of the aforementioned inflammatory cytokines can be useful in treating diseases associated with release of these cytokines. For example, WO 98/52558 discloses heteroaryl urea compounds which are indicated to be useful in treating cytokine mediated diseases. WO 99/23091 discloses another class of urea compounds which are useful as anti-inflammatory agents. WO 99/32463 relates to aryl ureas and their use in treating cytokine diseases and proteolytic enzyme mediated disease. WO 00/41698 discloses aryl ureas said to be useful in treating p38 MAP kinase diseases.

U.S. Pat. No. 5,162,360 discloses N-substituted aryl-N'-heterocyclic substituted urea compounds which are described as being useful for treating hypercholesterolemia and atherosclerosis.

The work cited above supports the principle that inhibition of cytokine production will be beneficial in the treatment acute and chronic inflammation in the lung caused by inhalation of smoke, endometriosis, Behcet's disease, uveitis, ankylosing spondylitis, pancreatitis, cancer, Lyme disease, restenosis following percutaneous transluminal coronary angioplasty, Alzheimer's disease, traumatic arthritis, sepsis, chronic obstructive pulmonary disease and congestive heart failure. None of these specific diseases have been taught or described in WO 00/55139 as being possible indications for the compounds taught therein. Therefore a need exists for small molecule inhibitors for treating these diseases with optimized efficacy, pharmacokinetic and safety profiles.

#### BRIEF SUMMARY OF THE INVENTION

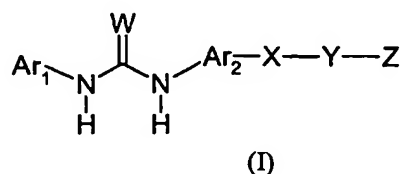
The present invention is directed a method of treating a cytokine mediated disease or condition chosen from: acute and chronic inflammation in the lung caused by inhalation of smoke, endometriosis, Behcet's disease, uveitis, ankylosing spondylitis, pancreatitis, cancer, Lyme Disease, restenosis following percutaneous transluminal coronary angioplasty, Alzheimer's disease, traumatic arthritis, sepsis, chronic obstructive pulmonary disease and congestive heart failure, said method comprising administering to a patient in need of such treatment a therapeutically effective amount of compounds disclosed in in WO 00/55139.

#### DETAILED DESCRIPTION OF THE INVENTION

In a first broad generic aspect, the present invention is directed a method of treating a cytokine mediated disease or condition chosen from: acute and chronic inflammation in the lung caused by inhalation of smoke, endometriosis, Behcet's disease, uveitis, ankylosing spondylitis, pancreatitis, cancer, Lyme disease, restenosis following percutaneous transluminal coronary angioplasty, Alzheimer's disease, traumatic arthritis, sepsis, chronic obstructive pulmonary disease and congestive heart failure, said method comprising administering to a patient in need of such treatment a therapeutically effective



amount of a compound of the formula (I) disclosed in WO 00/55139 which is the PCT case of US application serial no. 09/505,582 (both of which are incorporated by reference herein in their entirety):



wherein:

Ar<sub>1</sub> is selected from the group consisting of:

15  
pyrrole, pyrrolidine, pyrazole, imidazole, oxazole, thiazole, furan and thiophene;  
wherein Ar<sub>1</sub> may be substituted by one or more R<sub>1</sub>, R<sub>2</sub> or R<sub>3</sub>;

Ar<sub>2</sub> is:

20  
phenyl, naphthyl, quinoline, isoquinoline, tetrahydronaphthyl, tetrahydroquinoline,  
tetrahydroisoquinoline, benzimidazole, benzofuran, indanyl, indenyl or indole each being  
optionally substituted with zero to three R<sub>2</sub> groups;

X is:

25  
a) a C<sub>5-8</sub> cycloalkyl or cycloalkenyl optionally substituted with 0-2 oxo groups or 0-3 C<sub>1-4</sub>  
branched or unbranched alkyl, C<sub>1-4</sub> alkoxy or C<sub>1-4</sub> alkylamino chains;  
b) phenyl, furan, thiophene, pyrrole, imidazolyl, pyridine, pyrimidine, pyridinone,  
dihydropyridinone, maleimide, dihydromaleimide, piperidine, piperazine or pyrazine each  
30 being optionally independently substituted with 0-3 C<sub>1-4</sub> branched or unbranched alkyl,  
C<sub>1-4</sub>alkoxy, hydroxy, nitrile, mono- or di-(C<sub>1-3</sub> alkyl)amino, C<sub>1-6</sub> alkyl-S(O)<sub>m</sub>, or halogen;

Y is:

a bond or a C<sub>1-4</sub> saturated or unsaturated branched or unbranched carbon chain optionally partially or fully halogenated, wherein one or more methylene groups are optionally replaced by O, NH, S(O), S(O)<sub>2</sub> or S and wherein Y is optionally independently substituted with 0-2 oxo groups and one or more C<sub>1-4</sub> branched or unbranched alkyl which may be substituted by one or more halogen atoms;

Z is:

10

- a) phenyl, pyridine, pyrimidine, pyridazine, imidazole, furan, thiophene, pyran, which are optionally substituted with one to three groups consisting of halogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, hydroxy, mono- or di-(C<sub>1-3</sub> alkyl)amino, C<sub>1-6</sub> alkyl-S(O)<sub>m</sub>, COOH and phenylamino wherein the phenyl ring is optionally substituted with one to two groups consisting of halogen, C<sub>1-6</sub> alkyl and C<sub>1-6</sub> alkoxy;
- b) tetrahydropyran, tetrahydrofuran, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine sulfoxide, piperidine, piperidinone, piperazine, tetrahydropyrimidone, cyclohexanone, cyclohexanol, pentamethylene sulfide, pentamethylene sulfoxide, pentamethylene sulfone, tetramethylene sulfide, tetramethylene sulfoxide or tetramethylene sulfone which are optionally substituted with one to three groups consisting of nitrile, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, hydroxy, mono- or di-(C<sub>1-3</sub> alkyl)amino-C<sub>1-3</sub> alkyl, phenylamino-C<sub>1-3</sub> alkyl and C<sub>1-3</sub> alkoxy-C<sub>1-3</sub> alkyl;
- c) C<sub>1-6</sub> alkoxy, secondary or tertiary amine wherein the amino nitrogen is covalently bonded to groups selected from the group consisting of C<sub>1-3</sub> alkyl, C<sub>1-5</sub> alkoxyalkyl, pyridinyl-C<sub>1-3</sub> alkyl, imidazolyl-C<sub>1-3</sub> alkyl, tetrahydrofuranyl-C<sub>1-3</sub> alkyl, phenylamino, wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkoxy, hydroxy or mono- or di-(C<sub>1-3</sub> alkyl)amino, C<sub>1-6</sub> alkyl-S(O)<sub>m</sub>, and phenyl-S(O)<sub>m</sub>, wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkoxy, hydroxy or mono- or di-(C<sub>1-3</sub> alkyl)amino;

30

R<sub>1</sub> is :

- (a) C<sub>3-10</sub> branched or unbranched alkyl optionally partially or fully halogenated and optionally substituted with one to three phenyl, naphthyl or heterocyclic groups selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl; each such phenyl, naphthyl or heterocycle selected from the group hereinabove described in this paragraph, and being substituted with 0 to 5 groups selected from the group consisting of halogen, C<sub>1-6</sub> branched or unbranched alkyl which is optionally partially or fully halogenated, C<sub>3-8</sub> cycloalkyl, C<sub>5-8</sub> cycloalkenyl, hydroxy, nitrile, C<sub>1-3</sub> alkyloxy which is optionally partially or fully halogenated, NH<sub>2</sub>C(O) and di(C<sub>1-3</sub>)alkylaminocarbonyl;
- (b) C<sub>3-7</sub> cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl each being optionally be partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl groups, or an analog of such cycloalkyl group wherein one to three ring methylene groups are replaced by groups independently selected from the group consisting of O, S, CHOH, >C=O, >C=S and NH;
- (c) C<sub>3-10</sub> branched alkenyl optionally partially or fully halogenated and optionally substituted with one to three C<sub>1-5</sub> branched or unbranched alkyl, phenyl, naphthyl or heterocyclic groups, with each such heterocyclic group being independently selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl, and each such phenyl, naphthyl or heterocyclic group being substituted with 0 to 5 groups selected from the group consisting of halogen, C<sub>1-6</sub> branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, hydroxy, nitrile, C<sub>1-3</sub> alkoxy which is optionally partially or fully halogenated, NH<sub>2</sub>C(O) and mono- or di(C<sub>1-3</sub>)alkylaminocarbonyl;
- (d) a C<sub>5-7</sub> cycloalkenyl selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and

bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C<sub>1-3</sub> alkyl groups;

(e) nitrile; or

(f) C<sub>1-6</sub> branched or unbranched alkoxy carbonyl, C<sub>1-6</sub> branched or unbranched

5 alkylaminocarbonyl, C<sub>1-6</sub> branched or unbranched alkylcarbonylamino-C<sub>1-3</sub>-alkyl;

R<sub>2</sub> is:

a C<sub>1-6</sub> branched or unbranched alkyl optionally partially or fully halogenated, acetyl,

10 aroyl, C<sub>1-4</sub> branched or unbranched alkoxy optionally partially or fully halogenated, halogen, methoxycarbonyl or phenylsulfonyl;

R<sub>3</sub> is:

15 a) phenyl, naphthyl or heterocyclic group selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, tetrahydrofuryl, isoxazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl, 20 quinoxalinyl, quinazolinyl, purinyl and indazolyl, wherein such phenyl, naphthyl or heterocyclic group is optionally substituted with one to five groups selected from the group consisting of phenyl, naphthyl, heterocycle selected from the group hereinabove described in this paragraph, C<sub>1-6</sub> branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentyl, 25 cyclohexyl, cycloheptyl, bicyclopentyl, bicyclohexyl, bicycloheptyl, phenyl C<sub>1-5</sub> alkyl, naphthyl C<sub>1-5</sub> alkyl, halogen, hydroxy, nitrile, C<sub>1-3</sub> alkyloxy which may optionally be partially or fully halogenated, phenyloxy, naphthyloxy, heteraryloxy wherein the heterocyclic moiety is selected from the group hereinabove described in this paragraph, nitro, amino, mono- or di-(C<sub>1-3</sub>)alkylamino, phenylamino, 30 naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group hereinabove described in this paragraph, NH<sub>2</sub>C(O), a mono- or di-(C<sub>1-</sub>

<sub>3</sub>)alkyl aminocarbonyl, C<sub>1-5</sub> alkyl-C(O)-C<sub>1-4</sub> alkyl, amino-C<sub>1-5</sub> alkyl, mono- or di-(C<sub>1-3</sub>)alkylamino-C<sub>1-5</sub> alkyl, amino-S(O)<sub>2</sub>, di-(C<sub>1-3</sub>)alkylamino-S(O)<sub>2</sub>, R<sub>4</sub>-C<sub>1-5</sub> alkyl, R<sub>5</sub>-C<sub>1-5</sub> alkoxy, R<sub>6</sub>-C(O)-C<sub>1-5</sub> alkyl and R<sub>7</sub>-C<sub>1-5</sub> alkyl(R<sub>8</sub>)N, carboxy-mono- or di-(C<sub>1-5</sub>)-alkyl-amino;

- 5 b) a fused aryl selected from the group consisting of benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl, or a fused heterocyclyl selected from the group consisting of cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine,
- 10 cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopentanobenzimidazole, cyclohexanobenzimidazole, cyclopentanobenzoxazole, cyclohexanobenzoxazole, cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanthiophene and
- 15 cyclohexanthiophene; wherein the fused aryl or fused heterocyclyl ring is substituted with 0 to 3 groups independently selected from the group consisting of phenyl, naphthyl and heterocyclyl selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, and isothiazolyl, C<sub>1-6</sub> branched or unbranched alkyl which is optionally
- 20 partially or fully halogenated, halogen, nitrile, C<sub>1-3</sub> alkoxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heterocyclyloxy wherein the heterocyclyl moiety is selected from the group hereinabove described in this paragraph, nitro, amino, mono- or di-(C<sub>1-3</sub>)alkylamino, phenylamino, naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group
- 25 hereinabove described in this paragraph, NH<sub>2</sub>C(O), a mono- or di-(C<sub>1-3</sub>)alkyl aminocarbonyl, C<sub>1-4</sub> alkyl-OC(O), C<sub>1-5</sub> alkyl-C(O)-C<sub>1-4</sub> branched or unbranched alkyl, an amino-C<sub>1-5</sub> alkyl, mono- or di-(C<sub>1-3</sub>)alkylamino-C<sub>1-5</sub> alkyl, R<sub>9</sub>-C<sub>1-5</sub> alkyl, R<sub>10</sub>-C<sub>1-5</sub> alkoxy, R<sub>11</sub>-C(O)-C<sub>1-5</sub> alkyl, and R<sub>12</sub>-C<sub>1-5</sub> alkyl(R<sub>13</sub>)N;
- c) cycloalkyl selected from the group consisting of cyclopentyl, cyclohexyl,
- 30 cycloheptyl, bicyclopentyl, bicyclohexyl and bicycloheptyl, wherein the cycloalkyl is

optionally partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl groups;

5 d) C<sub>5-7</sub> cycloalkenyl selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C<sub>1-3</sub> alkyl groups;

10 e) acetyl, aroyl, alkoxycarbonylalkyl or phenylsulfonyl; or

f) C<sub>1-6</sub> branched or unbranched alkyl optionally partially or fully halogenated;

or R<sub>1</sub> and R<sub>2</sub> taken together may optionally form a fused phenyl or pyridinyl ring;

15 each R<sub>8</sub> and R<sub>13</sub> is independently selected from the group consisting of: hydrogen and C<sub>1-4</sub> branched or unbranched alkyl optionally be partially or fully halogenated;

20 each R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub> and R<sub>12</sub> is independently selected from the group consisting of morpholine, piperidine, piperazine, imidazole and tetrazole;

m is 0, 1 or 2;

25 W is O or S and

the pharmaceutically acceptable derivatives thereof.

30 A preferred subgeneric aspect of the invention comprises a method of using the compounds of the formula(I) as provided above and wherein:

Ar<sub>2</sub> is naphthyl, tetrahydronaphthyl, indanyl or indenyl and  
W is O.

A more preferred subgeneric aspect of the invention comprises a method of using the  
5 compounds of the formula(I) as provided above and wherein:

Ar<sub>1</sub> is selected from thiophene and pyrazole;

X is C<sub>5-7</sub> cycloalkyl or C<sub>5-7</sub>cycloalkenyl optionally substituted with 0-2 oxo groups  
or 0-3 C<sub>1-4</sub> branched or unbranched alkyl, C<sub>1-4</sub> alkoxy or C<sub>1-4</sub> alkylamino; or X is phenyl,  
pyridine, tetrahydropyridine, pyrimidine, furan or thiophene each being optionally  
10 independently substituted with 0-3 C<sub>1-4</sub> branched or unbranched alkyl, C<sub>1-4</sub>alkoxy,  
hydroxy, nitrile, mono- or di-(C<sub>1-3</sub> alkyl)amino, C<sub>1-6</sub> alkyl-S(O)<sub>m</sub> or halogen;

R<sub>1</sub> is C<sub>1-4</sub>alkyl branched or unbranched, cyclopropyl or cyclohexyl optionally  
partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl  
groups;

15 R<sub>3</sub> is C<sub>1-4</sub>alkyl branched or unbranched, phenyl, pyrimidinyl, pyrazolyl or  
pyridinyl each being optionally substituted as described hereinabove in the broadest  
generic aspect, alkoxy-carbonylalkyl or cyclopropyl or cyclopentyl optionally substituted  
as described hereinabove in the broadest generic aspect.

20 A yet more preferred subgeneric aspect of the invention comprises a method of using the  
compounds of the formula (I), as described in the immediate previous paragraph,  
wherein:

Ar<sub>1</sub> is pyrazole;

X is cyclopentenyl, cyclohexenyl or cycloheptenyl, optionally substituted with an  
25 oxo group or 0-3 C<sub>1-4</sub> branched or unbranched alkyl, C<sub>1-4</sub>alkoxy or C<sub>1-4</sub>alkylamino; or X  
is phenyl, pyridine, furan or thiophene each being optionally independently substituted  
with 0-3 C<sub>1-4</sub> branched or unbranched alkyl, C<sub>1-4</sub>alkoxy, hydroxy, nitrile, mono- or di-(C<sub>1-3</sub>  
alkyl)amino, C<sub>1-6</sub> alkyl-S(O)<sub>m</sub> or halogen.

A yet further preferred subgeneric aspect of the invention comprises a method of using the compounds of the formula (I), as described in the immediate previous paragraph, and wherein:

Y is -CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>NH-, -CH<sub>2</sub>CH<sub>2</sub>NH- or a bond;

and

Z is

phenyl, imidazole, furan, piperazine, tetrahydropyran, morpholine, thiomorpholine, thiomorpholine sulfoxide, piperidine, pyridine, secondary or tertiary amine wherein the amino nitrogen is covalently bonded to groups selected from the group consisting of C<sub>1-3</sub> alkyl and C<sub>1-5</sub> alkoxyalkyl, phenylamino wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkoxy, hydroxy or mono- or di-(C<sub>1-3</sub> alkyl)amino, C<sub>1-6</sub> alkyl-S(O)<sub>m</sub> and phenyl-S(O)<sub>m</sub> wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkoxy, hydroxy or mono- or di-(C<sub>1-3</sub> alkyl)amino.

A further preferred subgeneric aspect of the invention comprises a method of using the compounds of the formula (I), as described in the immediate previous paragraph, and wherein:

Ar<sub>1</sub> is 5-*tert*-butyl-pyrazol-3-yl; wherein the pyrazole ring may be substituted by R<sub>3</sub>;

R<sub>3</sub> is C<sub>1-4</sub>alkyl branched or unbranched, phenyl, pyrimidinyl, pyrazolyl, pyridinyl each being optionally substituted as described hereinabove in the broadest generic aspect, alkoxy-carbonylalkyl or cyclopropyl or cyclopentyl optionally substituted as described hereinabove in the broadest generic aspect.

A still yet further preferred subgeneric aspect of the invention comprises a method of using the compounds of the formula (I), as described in the immediate previous paragraph, and wherein:

X is pyridinyl.



A still yet further preferred subgeneric aspect of the invention comprises a method of using the compounds of the formula (I), as described in the immediate previous paragraph, and wherein:

the pyridinyl is attached to Ar<sub>1</sub> via the 3-pyridinyl position.

5

The following compounds are representative of the compounds of formula(I) which may be useful in the novel methods described herein:

10 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(4-(morpholin-4-yl)phenyl)naphthalen-1-yl]urea;

1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(4-(morpholin-4-ylmethyl)phenyl)naphthalen-1-yl]urea;

15 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(4-(2-(morpholin-4-yl)ethyl)phenyl)naphthalen-1-yl]urea;

1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(4-dimethylaminophenyl)naphthalen-1-yl]urea;

20

1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(3-(morpholin-4-yl)phenyl)naphthalen-1-yl]urea;

25 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(3-(morpholin-4-ylmethyl)phenyl)naphthalen-1-yl]urea;

1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)naphthalen-1-yl]urea;

30 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(5-morpholin-4-ylmethyl-pyridin-2-yl)naphthalen-1-yl]urea;

1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(5-morpholin-4-ylmethyl-fur-2-yl)naphthalen-1-yl]urea;

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1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)naphthalen-1-yl]urea;

40 1-[5-*tert*-butyl-2-methyl-2H-pyrazol-3-yl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)naphthalen-1-yl]urea;

1-[5-*tert*-butyl-2-phenyl-2H-pyrazol-3-yl]-3-[4-(4-piperdin-1-ylmethyl-phenyl)naphthalen-1-yl]urea;

- 1-[5-*tert*-butyl-2-phenyl-2H-pyrazol-3-yl]-3-[4-(4-(4-methylpiperazin-1-yl)methylphenyl)naphthalen-1-yl]urea;
- 5 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(3,4-di(morpholin-4-ylmethyl)phenyl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-pyridin-4-ylmethylpyridin-3-yl)naphthalen-1-yl]urea;
- 10 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(1-oxo-thiomorpholin-4-ylmethyl)pyridin-3-yl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(1-oxo-thiomorpholin-4-ylmethyl)pyridin-3-yl)naphthalen-1-yl]urea;
- 15 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-tetrahydropyran-4-ylmethylpyridin-3-yl)naphthalen-1-yl]urea;
- 20 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(1-oxo-tetrahydrothiophen-3-ylmethyl)pyridin-3-yl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(imidazol-1-ylmethyl)pyridin-3-yl)naphthalen-1-yl]urea;
- 25 1-[2-(3-dimethylaminomethylphenyl)-5-(1-methyl-cyclohexyl)-2H-pyrazol-3-yl]-3-[4-(6-morpholin-4-ylmethylpyridin-3-yl)naphthalen-1-yl]urea;
- 1-[2-(5-(1-methyl-cyclohexyl)-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-morpholin-4-ylmethylpyridin-3-yl)naphthalen-1-yl]urea;
- 30 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(2-morpholin-4-ylmethylpyrimidin-5-yl)naphthalen-1-yl]urea;
- 35 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-methoxy-5-(2-morpholin-4-yl-ethoxy)phenyl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(2-morpholin-4-yl-ethoxy)phenyl)naphthalen-1-yl]urea;
- 40 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-3-(dimethylamino)phenyl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-3-(methylsulfonyl)phenyl)naphthalen-1-yl]urea;
- 45

5-*tert*-butyl-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)naphthalen-1-yl]ureido}thiophene-2-carboxylic acid methyl ester;

5 5-*tert*-butyl-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)naphthalen-1-yl]ureido}thiophene-2-carboxylic acid methylamide;

5-*tert*-butyl-1-methyl-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)naphthalen-1-yl]ureido}-1H-pyrrole-2-carboxylic acid methyl ester;

10 5-*tert*-butyl-1-methyl-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)naphthalen-1-yl]ureido}-1H-pyrrole-2-carboxylic acid methylamide;

2-acetyl-amino N-(5-*tert*-butyl-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)naphthalen-1-yl]ureido}thiophen-2-ylmethyl)acetamide;

15 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(3-morpholin-4-yl-cyclohex-1-enyl)naphthalen-1-yl]urea;

20 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(3-morpholin-4-yl-cyclohept-1-enyl)naphthalen-1-yl]urea;

1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(3-(2-morpholin-4-yl-ethylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;

25 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(3-morpholin-4-yl-cyclohept-1-enyl)naphthalen-1-yl]urea;

1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(pyridin-4-yl-methylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;

30 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(dimethylaminoethylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;

35 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(pyridin-3-yl-methylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;

1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(phenyl-methylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;

40 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(2-phenylethylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;

1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(furan-2-yl-methylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;

45

- 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(2-pyridin-2-yl-ethylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;
- 5 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(2-piperdin-1-yl-ethylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(2-imidazol-4-yl-ethylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;
- 10 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(pyridin-2-yl-methylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(2-(4-methoxyphenyl)ethylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;
- 15 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(4-morpholin-4-ylmethyl-3-oxo-cyclohex-1-enyl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(4-(1-oxo-tetrahydrothiophen-3-ylmethyl)-3-oxo-cyclohex-1-enyl)naphthalen-1-yl]urea;
- 20 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(4-(1-oxo-thiomorpholin-4-ylmethyl)-3-oxo-cyclohex-1-enyl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(4-methylpiperazin-1-ylmethyl)-3-oxo-cyclohex-1-enyl)naphthalen-1-yl]urea;
- 25 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-{6-oxo-1-(tetrahydro-pyran-4-ylmethyl)-1,2,3,6-tetrahydro-pyridin-4-yl}naphthalen-1-yl]urea;
- 30 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(2-oxo-1-pyridin-4-ylmethyl-piperdin-4-yl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(6-oxo-1-pyridin-4-yl-1,2,3,6-tetrahydro-pyridin-4-yl)naphthalen-1-yl]urea;
- 35 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-oxo-1-pyridin-4-yl-1,2,3,6-tetrahydro-pyridin-4-yl)naphthalen-1-yl]urea;
- 40 5-*tert*-butyl-3-{3-[4-(6-oxo-1-pyridin-4-yl-1,2,3,6-tetrahydro-pyridin-4-yl)naphthalen-1-yl]ureido}thiophene-2-carboxylic acid methyl ester;
- 5-*tert*-butyl-1-methyl-3-{3-[4-(6-oxo-1-pyridin-4-yl-1,2,3,6-tetrahydro-pyridin-4-yl)naphthalen-1-yl]ureido}pyrrole-2-carboxylic acid methyl ester;
- 45

5-*tert*-butyl-1-methyl-3-{3-[4-(6-oxo-1-pyridin-4-yl-1,2,3,6-tetrahydro-pyridin-4-yl)naphthalen-1-yl]ureido}pyrrole-2-carboxylic acid methyl amide;

5-*tert*-butyl-3-{3-[4-(3-morpholin-4-yl-cyclohex-1-enyl)naphthalen-1-yl]ureido}thiophene-2-carboxylic acid methyl ester;

5-*tert*-butyl-1-methyl-3-{3-[4-(3-morpholin-4-yl-cyclohex-1-enyl)naphthalen-1-yl]ureido}pyrrole-2-carboxylic acid methyl ester; and

5-*tert*-butyl-1-methyl-3-{3-[4-(3-morpholin-4-yl-cyclohex-1-enyl)naphthalen-1-yl]ureido}pyrrole-2-carboxylic acid methyl amide and

the pharmaceutically acceptable derivatives thereof.

In another embodiment of the invention there are provided the following compounds of formula(I) which may be useful in the novel methods described herein:

1-[5-*tert*-butyl-2-(2-methoxypyridin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-*tert*-butyl-2-(2-methylthiopyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-*tert*-butyl-2-(2-methoxypyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-*tert*-butyl-2-(2-methylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[3-*tert*-butyl-1'-H-[1,4']bipyrazol-5-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[3-*tert*-butyl-1'-methyl-1'-H-[1,4']bipyrazol-5-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[3-*tert*-butyl-1'-(3-methylsulfonylpropyl)-1'-H-[1,4']bipyrazol-5-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[3-*tert*-butyl-1'-methyl-1'-H-[1,4']bipyrazol-5-yl]-3-[4-(6-(morpholin-4-yl-methyl)phenyl)naphthalen-1-yl]-urea;

1-[5-*tert*-butyl-2-(2-methoxypyridin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(pyridin-3-yl-methyl)pyridin-3-yl)naphthalen-1-yl]urea;

1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(4-(morpholin-4-yl-methyl)phenyl)naphthalen-1-yl]urea;

1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(4-(2-(morpholin-4-yl)ethyl)phenyl)naphthalen-1-yl]urea;

1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(3-(morpholin-4-yl-methyl)phenyl)naphthalen-1-yl]urea;

1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)naphthalen-1-yl]urea;

1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(5-morpholin-4-ylmethyl-pyridin-2-yl)naphthalen-1-yl]urea;

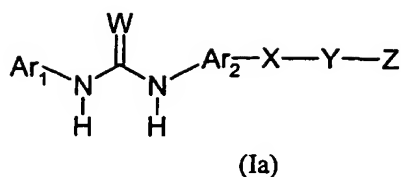
1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(5-morpholin-4-ylmethyl-fur-2-yl)naphthalen-1-yl]urea;

1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)naphthalen-1-yl]urea;

1-[5-*tert*-butyl-2-methyl-2H-pyrazol-3-yl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)naphthalen-1-yl]urea and

the pharmaceutically acceptable derivatives thereof.

In a second broad generic aspect, there is provided a method of treating a cytokine mediated disease or condition chosen from: acute and chronic inflammation in the lung caused by inhalation of smoke, endometriosis, Behcet's disease, uveitis, ankylosing spondylitis, pancreatitis, cancer, Lyme disease, restenosis following percutaneous transluminal coronary angioplasty, Alzheimer's disease, traumatic arthritis, sepsis, chronic obstructive pulmonary disease and congestive heart failure, said method comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of the formula (Ia) disclosed in WO 00/55139 which is the PCT case of US application serial no. 09/505,582:



wherein:

Ar<sub>1</sub> is:

pyrrole, pyrrolidine, pyrazole, imidazole, oxazole, thiazole, furan and thiophene;

wherein Ar<sub>1</sub> is optionally substituted by one or more R<sub>1</sub>, R<sub>2</sub> or R<sub>3</sub>;

Ar<sub>2</sub> is:

phenyl, naphthyl, quinoline, isoquinoline, tetrahydronaphthyl, tetrahydroquinoline,

tetrahydroisoquinoline, benzimidazole, benzofuran, indanyl, indenyl and indole each being optionally substituted with zero to three R<sub>2</sub> groups;

X is:

a C<sub>5-8</sub> cycloalkyl or cycloalkenyl optionally substituted with one to two oxo groups or one to three C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy or C<sub>1-4</sub> alkylamino chains each being branched or unbranched;

phenyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyridinyl, tetrahydropyridinyl, pyrimidinyl, pyridinonyl, dihydropyridinonyl, maleimidyl, dihydromaleimidyl, piperdinyl, benzimidazole, 3H-imidazo[4,5-b]pyridine, piperazinyl, pyridazinyl or pyrazinyl; each being optionally independently substituted with one to three C<sub>1-4</sub> alkyl, C<sub>1-4</sub>alkoxy, hydroxy, nitrile, amino, mono- or di-(C<sub>1-3</sub> alkyl)amino, mono- or di-(C<sub>1-3</sub> alkylamino)carbonyl, NH<sub>2</sub>C(O), C<sub>1-6</sub> alkyl-S(O)<sub>m</sub> or halogen;

Y is:

a bond or a C<sub>1-4</sub> saturated or unsaturated branched or unbranched carbon chain optionally partially or fully halogenated, wherein one or more C atoms are optionally replaced by O, N, or S(O)<sub>m</sub> and wherein Y is optionally independently substituted with one to two oxo groups, nitrile, phenyl, hydroxy or one or more C<sub>1-4</sub> alkyl optionally substituted by one or more halogen atoms;

Z is:

aryl, indanyl, heteroaryl selected from benzimidazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl and pyranyl, heterocycle selected from piperazinyl, tetrahydropyrimidinyl, cyclohexanonyl, cyclohexanolyl, 2-oxa- or 2-thia-5-aza-bicyclo[2.2.1]heptanyl, pentamethylene sulfidyl, pentamethylene sulfoxidyl, pentamethylene sulfonyl, tetramethylene sulfidyl, tetramethylene sulfoxidyl or tetramethylene sulfonyl, tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxolanonyl, 1,3-dioxanonyl, 1,4-dioxanyl, morpholino, thiomorpholino, thiomorpholino sulfoxidyl, thiomorpholino sulfonyl, piperidinyl, piperidinonyl, pyrrolidinyl and dioxolanyl, each of the aforementioned Z are optionally substituted with one to three halogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>1-3</sub> alkoxy-C<sub>1-3</sub> alkyl, C<sub>1-6</sub> alkoxycarbonyl, aroyl, heteroaroyl, heterocycleC<sub>1-3</sub>acyl wherein the heteroaryl and heterocycle are as defined hereinabove in this paragraph, C<sub>1-3</sub>acyl, oxo, hydroxy, pyridinyl-C<sub>1-3</sub> alkyl, imidazolyl-C<sub>1-3</sub> alkyl, tetrahydrofuranyl-C<sub>1-3</sub> alkyl, nitrile-C<sub>1-3</sub> alkyl, nitrile, carboxy, phenyl wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkoxy, hydroxy or mono- or di-(C<sub>1-3</sub> alkyl)amino, amino-S(O)<sub>m</sub>, C<sub>1-6</sub> alkyl-S(O)<sub>m</sub> or phenyl-S(O)<sub>m</sub> wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkoxy, hydroxy, halogen or mono- or di-(C<sub>1-3</sub> alkyl)amino; or Z is optionally substituted with one to three amino, aminocarbonyl or amino-C<sub>1-3</sub> alkyl wherein the N atom is optionally independently mono- or di-substituted by aminoC<sub>1-6</sub>alkyl, C<sub>1-3</sub>alkyl, arylC<sub>0-3</sub>alkyl, C<sub>1-5</sub> alkoxyC<sub>1-3</sub> alkyl, C<sub>1-5</sub> alkoxy, aroyl, C<sub>1-3</sub>acyl, C<sub>1-3</sub>alkyl-S(O)<sub>m</sub>- or arylC<sub>0-3</sub>alkyl-S(O)<sub>m</sub>- each of the aforementioned alkyl and aryl attached



to the amino group is optionally substituted with one to two halogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, hydroxy or mono- or di-(C<sub>1-3</sub> alkyl)amino;

or Z is optionally substituted with one to three aryl, heterocycle or heteroaryl as hereinabove described in this paragraph each in turn is optionally substituted by halogen,  
 5 C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy;

or Z is hydroxy, hydroxyC<sub>1-3</sub>alkyl, halogen, nitrile, amino wherein the N atom is optionally independently mono- or di-substituted by C<sub>1-6</sub>alkyl, aminoC<sub>1-6</sub>alkyl, arylC<sub>0-3</sub>alkyl, C<sub>1-5</sub> alkoxyC<sub>1-3</sub> alkyl, C<sub>1-5</sub> alkoxy, aroyl, C<sub>1-3</sub>acyl, C<sub>1-3</sub>alkyl-S(O)<sub>m</sub><sup>-</sup>, arylC<sub>0-3</sub>alkyl-S(O)<sub>m</sub><sup>-</sup>, nitrileC<sub>1-4</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>1-3</sub>alkyl, each of the aforementioned alkyl and aryl  
 10 attached to the amino group is optionally substituted with one to two halogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, hydroxy or mono- or di-(C<sub>1-3</sub> alkyl)amino, C<sub>1-6</sub> alkoxyheteroarylC<sub>0-3</sub>alkyl, heteroarylC<sub>0-3</sub>alkyl or heterocyclylC<sub>0-3</sub>alkyl wherein the heteroaryl and heterocycle is hereinabove described in this paragraph,  
 15 or Z is C<sub>1-6</sub>alkyl branched or unbranched, C<sub>1-6</sub>alkoxy, C<sub>1-3</sub>acylamino, nitrileC<sub>1-4</sub>alkyl, C<sub>1-6</sub> alkyl-S(O)<sub>m</sub>, and phenyl-S(O)<sub>m</sub>, wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkoxy, hydroxy or mono- or di-(C<sub>1-3</sub> alkyl)amino;

R<sub>1</sub> is :

20

- a) C<sub>1-10</sub> branched or unbranched alkyl optionally partially or fully halogenated, and optionally substituted with one to three phenyl, naphthyl or heterocyclic groups selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl; each such phenyl,  
 25 naphthyl or heterocycle, selected from the group hereinabove described, being substituted with 0 to 5 groups selected from the group consisting of halogen, C<sub>1-6</sub> branched or unbranched alkyl which is optionally partially or fully halogenated, C<sub>3-8</sub> cycloalkyl, C<sub>5-8</sub> cycloalkenyl, hydroxy, nitrile, C<sub>1-3</sub> alkyloxy which is optionally partially or fully halogenated, NH<sub>2</sub>C(O) and di(C<sub>1-3</sub>)alkylaminocarbonyl;
- 30 b) C<sub>3-7</sub> cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclopentyl, bicyclohexyl and bicycloheptyl,

each optionally partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl groups, or an analog of such cycloalkyl group wherein one to three ring methylene groups are replaced by groups independently selected from the group consisting of O, S, CHOH, >C=O, >C=S and NH;

- 5 c) C<sub>3-10</sub> branched alkenyl optionally partially or fully halogenated and optionally substituted with one to three C<sub>1-5</sub> branched or unbranched alkyl, phenyl, naphthyl or heterocyclic groups, with each such heterocyclic group being independently selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl, and each such phenyl, naphthyl or heterocyclic group being substituted with 0 to 5 groups selected from the group consisting of halogen, C<sub>1-6</sub> branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, hydroxy, nitrile, C<sub>1-3</sub> alkoxy which is optionally partially or fully halogenated, NH<sub>2</sub>C(O) and mono- or di(C<sub>1-3</sub>)alkylaminocarbonyl;
- 10 d) a C<sub>5-7</sub> cycloalkenyl selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C<sub>1-3</sub> alkyl groups;
- 15 e) nitrile; or
- 20 f) C<sub>1-6</sub> branched or unbranched alkoxy carbonyl, C<sub>1-6</sub> branched or unbranched alkylaminocarbonyl, C<sub>1-6</sub> branched or unbranched alkylcarbonylamino-C<sub>1-3</sub>-alkyl;

R<sub>2</sub> is:

- 25 a C<sub>1-6</sub> branched or unbranched alkyl optionally partially or fully halogenated and optionally substituted with nitrile,
- or R<sub>2</sub> is acetyl, aroyl, C<sub>1-4</sub> branched or unbranched alkoxy optionally partially or fully halogenated, halogen, methoxycarbonyl or phenylsulfonyl;

30

R<sub>3</sub> is:

- a) phenyl, naphthyl or heterocyclic group selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, tetrahydrofuryl, isoxazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl, quinoxalinyl, quinazolinyl, purinyl and indazolyl, wherein such phenyl, naphthyl or heterocyclic group is optionally substituted with one to five groups selected from the group consisting of a phenyl, naphthyl, heterocycle selected from the group hereinabove described in this paragraph, C<sub>1-6</sub> branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclopentyl, bicyclohexyl, bicycloheptyl, phenyl C<sub>1-5</sub> alkyl, naphthyl C<sub>1-5</sub> alkyl, halogen, hydroxy, oxo, nitrile, C<sub>1-3</sub> alkoxy optionally partially or fully halogenated, C<sub>1-3</sub> alkoxyC<sub>1-5</sub>alkyl, C<sub>1-3</sub>thioalkyl, C<sub>1-3</sub>thioalkylC<sub>1-5</sub>alkyl, phenyloxy, naphthyloxy, heteraryloxy wherein the heterocyclic moiety is selected from the group hereinabove described in this paragraph, nitro, amino, mono- or di-(C<sub>1-3</sub>)alkylamino, phenylamino, naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group hereinabove described in this paragraph, NH<sub>2</sub>C(O), a mono- or di-(C<sub>1-3</sub>)alkyl aminocarbonyl, C<sub>1-5</sub> alkyl-C(O)-C<sub>1-4</sub> alkyl, amino-C<sub>1-5</sub> alkyl, mono- or di-(C<sub>1-3</sub>)alkylamino-C<sub>1-5</sub> alkyl, amino-S(O)<sub>2</sub>, di-(C<sub>1-3</sub>)alkylamino-S(O)<sub>2</sub>, R<sub>4</sub>-C<sub>1-5</sub> alkyl, R<sub>5</sub>-C<sub>1-5</sub> alkoxy, R<sub>6</sub>-C(O)-C<sub>1-5</sub> alkyl and R<sub>7</sub>-C<sub>1-5</sub> alkyl(R<sub>8</sub>)N, carboxy-mono- or di-(C<sub>1-5</sub>)-alkyl-amino;
- b) a fused aryl selected from the group consisting of benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl, or a fused heterocyclyl selected from the group consisting of cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopentanobenzimidazole, cyclohexanobenzimidazole, cyclopentanobenzoxazole, cyclohexanobenzoxazole,

- cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanthiophene and cyclohexanthiophene; wherein the fused aryl or fused heterocyclyl ring is substituted with 0 to 3 groups independently selected from the group consisting of phenyl, naphthyl and heterocyclyl selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, and isothiazolyl, C<sub>1-6</sub> branched or unbranched alkyl which is optionally partially or fully halogenated, halogen, nitrile, C<sub>1-3</sub> alkoxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heterocyclyloxy wherein the heterocyclyl moiety is selected from the group hereinabove described, nitro, amino, mono- or di-(C<sub>1-3</sub>)alkylamino, phenylamino, naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group hereinabove described, NH<sub>2</sub>C(O), a mono- or di-(C<sub>1-3</sub>)alkyl aminocarbonyl, C<sub>1-4</sub> alkyl-OC(O), C<sub>1-5</sub> alkyl-C(O)-C<sub>1-4</sub> branched or unbranched alkyl, an amino-C<sub>1-5</sub> alkyl, mono- or di-(C<sub>1-3</sub>)alkylamino-C<sub>1-5</sub> alkyl, R<sub>9</sub>-C<sub>1-5</sub> alkyl, R<sub>10</sub>-C<sub>1-5</sub> alkoxy, R<sub>11</sub>-C(O)-C<sub>1-5</sub> alkyl and R<sub>12</sub>-C<sub>1-5</sub> alkyl(R<sub>13</sub>)N;
- 15 c) cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclopentyl, bicyclohexyl and bicycloheptyl, wherein the cycloalkyl is optionally partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl groups;
- 20 d) C<sub>5-7</sub> cycloalkenyl selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C<sub>1-3</sub> alkyl groups;
- 25 e) acetyl, aroyl, C<sub>1-6</sub>alkoxycarbonylC<sub>1-6</sub>alkyl or phenylsulfonyl; or
- f) C<sub>1-6</sub> branched or unbranched alkyl optionally partially or fully halogenated;

or R<sub>1</sub> and R<sub>2</sub> taken together optionally form a fused phenyl or pyridinyl ring;

30

each R<sub>8</sub> and R<sub>13</sub> is independently selected from the group consisting of:

hydrogen and C<sub>1-4</sub> branched or unbranched alkyl optionally partially or fully halogenated;

5 each R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub> and R<sub>12</sub> is independently selected from the group consisting of morpholine, piperidine, piperazine, imidazole and tetrazole;

m is 0, 1 or 2;

W is O or S;

10

wherein X is directly attached to one or two -Y-Z, and the pharmaceutically acceptable derivatives thereof.

15 A preferred subgeneric aspect of the invention comprises a method of using the compounds of the formula(Ia) as provided above and wherein:

20 Ar<sub>2</sub> is naphthyl, tetrahydronaphthyl, indanyl or indenyl and W is O.

A more preferred subgeneric aspect of the invention comprises a method of using the compounds of the formula(Ia) as provided above and wherein:

25

Ar<sub>1</sub> is thiophene or pyrazole each substituted independently by one to three R<sub>1</sub>, R<sub>2</sub> or R<sub>3</sub>;

X is:

a C<sub>3-7</sub> cycloalkyl or cycloalkenyl optionally substituted with one to two oxo groups or one to three C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy or C<sub>1-4</sub> alkylamino chains each being branched or unbranched;

5 phenyl, indanyl, furanyl, thienyl, imidazolyl, pyridinyl, pyrazinyl, tetrahydropyridinyl, pyrimidinyl, pyridinonyl, piperdinyl, benzimidazole or piperazinyl; each being optionally independently substituted with one to three C<sub>1-4</sub> alkyl, C<sub>1-4</sub>alkoxy, hydroxy, nitrile, amino, mono- or di-(C<sub>1-3</sub> alkyl)amino, mono- or di-(C<sub>1-3</sub> alkylamino)carbonyl, NH<sub>2</sub>C(O), C<sub>1-6</sub> alkyl-S(O)<sub>m</sub> or halogen;

10

Y is:

a bond or a C<sub>1-4</sub> saturated or unsaturated branched or unbranched carbon chain optionally partially or fully halogenated, wherein one or more C atoms are optionally replaced by O  
15 or N, and wherein Y is optionally independently substituted with one to two oxo groups, nitrile, phenyl, hydroxy or one or more C<sub>1-4</sub> alkyl optionally substituted by one or more halogen atoms;

Z is:

20

phenyl, heteroaryl selected from pyridinyl, imidazolyl, furanyl and thienyl, heterocycle selected from piperazinyl, 2-oxa-5-aza-bicyclo[2.2.1]heptanyl, pentamethylene sulfidyl, pentamethylene sulfoxidyl, pentamethylene sulfonyl, tetrahydrofuranyl, morpholino, thiomorpholino and piperidinyl,

25 each of the aforementioned Z are optionally substituted with one to three halogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>1-3</sub> alkoxy-C<sub>1-3</sub> alkyl, C<sub>1-6</sub> alkoxycarbonyl, aroyl, morpholinocarbonyl, C<sub>1-3</sub>acyl, oxo, hydroxy, pyridinyl-C<sub>1-3</sub> alkyl, imidazolyl-C<sub>1-3</sub> alkyl, tetrahydrofuranyl-C<sub>1-3</sub> alkyl, nitrile-C<sub>1-3</sub> alkyl, nitrile, carboxy, phenyl wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkoxy, hydroxy or mono- or  
30 di-(C<sub>1-3</sub> alkyl)amino, amino-S(O)<sub>m</sub>, C<sub>1-6</sub> alkyl-S(O)<sub>m</sub> or phenyl-S(O)<sub>m</sub> wherein the phenyl

ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkoxy, hydroxy, halogen or mono- or di-(C<sub>1-3</sub> alkyl)amino;

or Z is optionally substituted with one to three amino, aminocarbonyl or amino-C<sub>1-3</sub> alkyl wherein the N atom is optionally independently mono- or di-substituted by aminoC<sub>1-</sub>

5   <sub>6</sub>alkyl, C<sub>1-3</sub>alkyl, arylC<sub>0-3</sub>alkyl, C<sub>1-5</sub> alkoxyC<sub>1-3</sub> alkyl, C<sub>1-5</sub> alkoxy, aroyl, C<sub>1-3</sub>acyl, C<sub>1-3</sub>alkyl-S(O)<sub>m</sub>- or arylC<sub>0-3</sub>alkyl-S(O)<sub>m</sub>- each of the aforementioned alkyl and aryl attached to the amino group are optionally substituted with one to two halogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy;

or Z is optionally substituted with one to three aryl, heterocycle or heteroaryl as

10   hereinabove described in this paragraph each in turn is optionally substituted by halogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy;

or Z is hydroxy, hydroxyC<sub>1-3</sub>alkyl, halogen, nitrile, amino wherein the N atom is

optionally independently mono- or di-substituted by aroyl, C<sub>1-3</sub>acyl, C<sub>1-6</sub>alkyl, C<sub>1-5</sub>

15   alkoxyC<sub>1-3</sub> alkyl, pyridinylC<sub>1-3</sub>alkyl, tetrahydrofuranlylC<sub>1-3</sub>alkyl, nitrileC<sub>1-4</sub>alkyl or phenyl wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkoxy, hydroxy or mono- or di-(C<sub>1-3</sub> alkyl)amino,

or Z is C<sub>1-6</sub>alkyl branched or unbranched, C<sub>1-6</sub>alkoxy or nitrileC<sub>1-4</sub>alkyl;

20       R<sub>1</sub> is:

C<sub>1-4</sub> branched or unbranched alkyl optionally partially or fully halogenated;

cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl optionally partially or

25   fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl groups, or an analog of such cycloalkyl group wherein one to three ring methylene groups are replaced by groups independently selected from the group consisting of O, S and NH;

C<sub>3-10</sub> branched alkenyl optionally partially or fully halogenated and optionally substituted

30   with one to three C<sub>1-5</sub> branched or unbranched alkyl;

cyclopentenyl and cyclohexenyl optionally substituted with one to three C<sub>1-3</sub> alkyl groups;

R<sub>2</sub> is:

a C<sub>1-6</sub> branched or unbranched alkyl optionally partially or fully halogenated and optionally substituted with nitrile;

R<sub>3</sub> is:

phenyl or heterocyclic group selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl and pyrazolyl, wherein such phenyl or heterocyclic group is optionally substituted with one to five groups selected from the group consisting of a phenyl, heterocycle selected from the group hereinabove described in this paragraph, C<sub>1-6</sub> branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclopentyl, bicyclohexyl, bicycloheptyl, phenyl C<sub>1-5</sub> alkyl, naphthyl C<sub>1-5</sub> alkyl, halogen, hydroxy, oxo, nitrile, C<sub>1-3</sub> alkoxy optionally be partially or fully halogenated, C<sub>1-3</sub> alkoxyC<sub>1-5</sub>alkyl, C<sub>1-3</sub>thioalkyl, C<sub>1-3</sub>thioalkylC<sub>1-5</sub>alkyl, phenyloxy, naphthyloxy, heteraryloxy wherein the heterocyclic moiety is selected from the group hereinabove described in this paragraph, nitro, amino, mono- or di-(C<sub>1-3</sub>)alkylamino, phenylamino, naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group hereinabove described in this paragraph, NH<sub>2</sub>C(O), a mono- or di-(C<sub>1-3</sub>)alkyl aminocarbonyl, C<sub>1-5</sub> alkyl-C(O)-C<sub>1-4</sub> alkyl, amino-C<sub>1-5</sub> alkyl, mono- or di-(C<sub>1-3</sub>)alkylamino-C<sub>1-5</sub> alkyl, amino-S(O)<sub>2</sub>, di-(C<sub>1-3</sub>)alkylamino-S(O)<sub>2</sub>, R<sub>4</sub>-C<sub>1-5</sub> alkyl, R<sub>5</sub>-C<sub>1-5</sub> alkoxy, R<sub>6</sub>-C(O)-C<sub>1-5</sub> alkyl and R<sub>7</sub>-C<sub>1-5</sub> alkyl(R<sub>8</sub>)N, carboxy-mono- or di-(C<sub>1-5</sub>)-alkyl-amino;

a fused aryl selected from the group consisting of benzocyclobutanyl, indanyl, indenyl; wherein the fused aryl is substituted with 0 to 3 groups independently selected from the group consisting of phenyl, naphthyl and heterocyclyl selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl,



furyl, isoxazolyl, and isothiazolyl, C<sub>1-6</sub> branched or unbranched alkyl which is optionally partially or fully halogenated, halogen, nitrile, C<sub>1-3</sub> alkoxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heterocyclyloxy wherein the heterocyclyl moiety is selected from the group hereinabove described in this paragraph, nitro, amino, 5 mono- or di-(C<sub>1-3</sub>)alkylamino, phenylamino, naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group hereinabove described in this paragraph, NH<sub>2</sub>C(O), a mono- or di-(C<sub>1-3</sub>)alkyl aminocarbonyl, C<sub>1-4</sub> alkyl-OC(O), C<sub>1-5</sub> alkyl-C(O)-C<sub>1-4</sub> branched or unbranched alkyl, an amino-C<sub>1-5</sub> alkyl, mono- or di-(C<sub>1-3</sub>)alkylamino-C<sub>1-5</sub> alkyl, R<sub>9</sub>-C<sub>1-5</sub> alkyl, R<sub>10</sub>-C<sub>1-5</sub> alkoxy, R<sub>11</sub>-C(O)-C<sub>1-5</sub> alkyl and R<sub>12</sub>-C<sub>1-5</sub> alkyl(R<sub>13</sub>)N;

cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, wherein the cycloalkyl is optionally partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl groups;

C<sub>1-6</sub>alkoxycarbonylC<sub>1-6</sub>alkyl;

or R<sub>1</sub> and R<sub>2</sub> taken together optionally form a fused phenyl or pyridinyl ring;

each R<sub>8</sub> and R<sub>13</sub> is independently selected from the group consisting of: hydrogen and C<sub>1-4</sub> branched or unbranched alkyl optionally partially or fully halogenated; and

each R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub> and R<sub>12</sub> is independently selected from the group consisting of morpholine, piperidine, piperazine, imidazole and tetrazole;

wherein X is directly attached to one -Y-Z.

A yet more preferred subgeneric aspect of the invention comprises a method of using the compounds of the formula (Ia), as described in the immediate previous paragraph, wherein:

5       Ar<sub>1</sub> is pyrazole;

X is:

cyclopentenyl, cyclohexenyl, cycloheptenyl, optionally substituted with an oxo group or one to three C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy or C<sub>1-4</sub> alkylamino chains each being branched or  
10   unbranched;

phenyl, furanyl, thienyl, pyridinyl, pyrazinyl piperidinyl or pyrimidinyl each being optionally independently substituted with one to three C<sub>1-2</sub> alkyl, C<sub>1-2</sub>alkoxy, hydroxy or halogen;

15

Z is:

phenyl, heteroaryl selected from pyridinyl, imidazolyl and furanyl, heterocycle selected from 2-oxa-5-aza-bicyclo[2.2.1]heptanyl, pentamethylene sulfidyl, pentamethylene  
20   sulfoxidyl, pentamethylene sulfonyl, tetrahydrofuranyl, tetrahydropyranyl, piperazinyl, morpholino, thiomorpholino, thiomorpholino sulfoxide and piperidinyl, each of the aforementioned Z are optionally substituted with one to three halogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>1-3</sub> alkoxy-C<sub>1-3</sub> alkyl, C<sub>1-6</sub> alkoxy-carbonyl, aroyl, morpholinocarbonyl, C<sub>1-3</sub>acyl, oxo, hydroxy, pyridinyl-C<sub>1-3</sub> alkyl, imidazolyl-C<sub>1-3</sub> alkyl,  
25   tetrahydrofuranyl-C<sub>1-3</sub> alkyl, nitrile-C<sub>1-3</sub> alkyl, nitrile, carboxy, phenyl wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkoxy, hydroxy or mono- or di-(C<sub>1-3</sub> alkyl)amino, amino-S(O)<sub>m</sub>, C<sub>1-6</sub> alkyl-S(O)<sub>m</sub>, or phenyl-S(O)<sub>m</sub> wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkoxy, hydroxy, halogen or mono- or di-(C<sub>1-3</sub> alkyl)amino;  
30   or Z is optionally substituted with one to three amino, aminocarbonyl or amino-C<sub>1-3</sub> alkyl wherein the N atom is optionally independently mono- or di-substituted by aminoC<sub>1</sub>.

<sub>6</sub>alkyl, C<sub>1-3</sub>alkyl, arylC<sub>0-3</sub>alkyl, C<sub>1-5</sub>alkoxyC<sub>1-3</sub>alkyl, C<sub>1-5</sub>alkoxy, aroyl, C<sub>1-3</sub>acyl, C<sub>1-3</sub>alkyl-S(O)<sub>m</sub>, pyridinylC<sub>0-3</sub>alkyl, tetrahydrofuranylC<sub>0-3</sub>alkyl, or arylC<sub>0-3</sub>alkyl-S(O)<sub>m</sub>- each of the aforementioned alkyl and aryl attached to the amino group is optionally substituted with one to two halogen, C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy;

5

or Z is hydroxy, hydroxyC<sub>1-3</sub>alkyl, halogen, nitrile, amino wherein the N atom is optionally independently mono- or di-substituted by C<sub>1-6</sub>alkyl, pyridinylC<sub>0-3</sub>alkyl, tetrahydrofuranylC<sub>0-3</sub>alkyl, C<sub>1-5</sub>alkoxyC<sub>1-3</sub>alkyl, C<sub>1-3</sub>acyl, nitrileC<sub>1-4</sub>alkyl or phenyl wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub>alkoxy,

10 hydroxy or mono- or di-(C<sub>1-3</sub>alkyl)amino,

or Z is C<sub>1-6</sub>alkyl branched or unbranched, C<sub>1-6</sub>alkoxy or nitrileC<sub>1-4</sub>alkyl;

R<sub>1</sub> is:

15 C<sub>1-4</sub> branched or unbranched alkyl optionally partially or fully halogenated;

cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl and cycloheptanyl optionally partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub>alkyl groups, or an analog of such cycloalkyl group wherein one to three ring methylene groups are replaced by groups independently selected from the group consisting of O, S and NH;

20

C<sub>3-10</sub> branched alkenyl optionally partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub> branched or unbranched alkyl;

25 cyclopentenyl and cyclohexenyl optionally substituted with one to three C<sub>1-3</sub>alkyl groups;

R<sub>2</sub> is:

a C<sub>1-6</sub> branched or unbranched alkyl optionally partially or fully halogenated and optionally substituted with nitrile;

30

R<sub>3</sub> is:

phenyl or heterocyclic group selected from the group consisting of pyridinyl, pyrimidinyl, pyridazinyl and pyrazolyl, wherein such phenyl or heterocyclic group is optionally substituted with one to five groups selected from the group consisting of a phenyl, heterocycle selected from the group hereinabove described in this paragraph, C<sub>1-6</sub> branched or unbranched alkyl which is optionally partially or fully halogenated, phenyl C<sub>1-5</sub> alkyl, halogen, hydroxy, oxo, nitrile, C<sub>1-3</sub> alkoxy optionally partially or fully halogenated, C<sub>1-3</sub>thioalkyl, C<sub>1-3</sub>thioalkylC<sub>1-5</sub>alkyl, amino, mono- or di-(C<sub>1-3</sub>)alkylamino, NH<sub>2</sub>C(O) or a mono- or di-(C<sub>1-3</sub>)alkyl aminocarbonyl,

C<sub>1-6</sub>alkoxycarbonylC<sub>1-6</sub>alkyl;

or R<sub>3</sub> is cyclopropyl or cyclopentyl each optionally partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl groups

or R<sub>1</sub> and R<sub>2</sub> taken together optionally form a fused phenyl or pyridinyl ring.

A yet further preferred subgeneric aspect of the invention comprises a method of using the compounds of the formula (Ia), as described in the immediate previous paragraph, and wherein:

Y is -CH<sub>2</sub>-, -O-(CH<sub>2</sub>)<sub>0-3</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>NH-, -CH<sub>2</sub>CH<sub>2</sub>-NH-, NH-CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>-NH-CH<sub>2</sub>-, -NH-, -NH-C(O)-, -C(O)-, -CH(OH)-, -CH<sub>2</sub>(CH<sub>2</sub>CH<sub>3</sub>)- or a bond;

X is:

cyclohexenyl optionally substituted with an oxo group or one to three C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy or C<sub>1-4</sub> alkylamino chains each being branched or unbranched;

phenyl, pyridinyl, pyrazinyl, piperidinyl or pyrimidinyl each being optionally independently substituted with one to three C<sub>1-2</sub> alkyl, C<sub>1-2</sub>alkoxy, hydroxy or halogen;

Z is:

5

phenyl, heteroaryl selected from pyridinyl, imidazolyl and furanyl, heterocycle selected from 2-oxa-5-aza-bicyclo[2.2.1]heptanyl, pentamethylene sulfidyl, pentamethylene sulfoxidyl, pentamethylene sulfonyl, tetrahydrofuranyl, tetrahydropyranyl, piperazinyl, morpholino, thiomorpholino, thiomorpholino sulfoxide and piperidinyl,

10 each of the aforementioned Z are optionally substituted with one to three halogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>1-3</sub> alkoxy-C<sub>1-3</sub> alkyl, C<sub>1-6</sub> alkoxycarbonyl, aroyl, morpholinocarbonyl, C<sub>1-3</sub>acyl, oxo, hydroxy, pyridinyl-C<sub>1-3</sub> alkyl, imidazolyl-C<sub>1-3</sub> alkyl, tetrahydrofuranyl-C<sub>1-3</sub> alkyl, nitrile-C<sub>1-3</sub> alkyl, nitrile, carboxy, phenyl wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkoxy, hydroxy or mono- or  
15 di-(C<sub>1-3</sub> alkyl)amino, amino-S(O)<sub>m</sub>, C<sub>1-6</sub> alkyl-S(O)<sub>m</sub>, or phenyl-S(O)<sub>m</sub> wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkoxy, hydroxy, halogen or mono- or di-(C<sub>1-3</sub> alkyl)amino;

or Z is optionally substituted with one to three amino or aminocarbonyl wherein the N atom is optionally independently mono- or di-substituted by aminoC<sub>1-6</sub>alkyl, C<sub>1-3</sub>alkyl,  
20 arylC<sub>0-3</sub>alkyl, C<sub>1-5</sub> alkoxyC<sub>1-3</sub> alkyl, C<sub>1-5</sub> alkoxy, aroyl, C<sub>1-3</sub>acyl, C<sub>1-3</sub>alkyl-S(O)<sub>m</sub>- or arylC<sub>0-3</sub>alkyl-S(O)<sub>m</sub>- each of the aforementioned alkyl and aryl attached to the amino group is optionally substituted with one to two halogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy;

or Z is hydroxy, hydroxyC<sub>1-3</sub>alkyl, halogen, nitrile, amino wherein the N atom is  
25 optionally independently mono- or di-substituted by C<sub>1-3</sub>alkyl, pyridinylC<sub>1-2</sub>alkyl, tetrahydrofuranylC<sub>1-2</sub>alkyl, C<sub>1-3</sub> alkoxyC<sub>1-3</sub> alkyl, C<sub>1-3</sub>acyl, nitrileC<sub>1-4</sub>alkyl, phenyl wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkoxy, hydroxy or mono- or di-(C<sub>1-3</sub> alkyl)amino,

or Z is C<sub>1-6</sub>alkyl branched or unbranched, C<sub>1-6</sub>alkoxy or nitrileC<sub>1-4</sub>alkyl;

30

R<sub>1</sub> is:

C<sub>1-4</sub> branched or unbranched alkyl optionally partially or fully halogenated;

R<sub>2</sub> is:

5

a C<sub>1-3</sub> branched or unbranched alkyl optionally partially or fully halogenated and optionally substituted with nitrile;

R<sub>3</sub> is:

10

phenyl or heterocyclic group selected from the group consisting of pyridinyl, pyrimidinyl, and pyrazolyl, wherein such phenyl or heterocyclic group is optionally substituted with one to five groups selected from the group consisting of C<sub>1-3</sub> branched or unbranched alkyl which is optionally partially or fully halogenated, C<sub>1-3</sub> alkoxy which optionally partially or fully halogenated, C<sub>1-3</sub>thioalkyl, C<sub>1-3</sub>thioalkylC<sub>1-3</sub>alkyl, amino or NH<sub>2</sub>C(O);

15

C<sub>1-3</sub>alkoxycarbonyl;

or R<sub>3</sub> is cyclopropyl or cyclopentyl each optionally partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl groups.

20

A further preferred subgeneric aspect of the invention comprises a method of using the compounds of the formula (Ia), as described in the immediate previous paragraph, and wherein:

25

Ar<sub>1</sub> is 5-tert-butyl-pyrazol-3-yl; wherein the pyrazole ring is substituted independently by one to two R<sub>2</sub> or R<sub>3</sub>;

X is:

cyclohexenyl;

30

phenyl, pyridinyl, pyrazinyl, piperidinyl or pyrimidinyl each being optionally independently substituted with C<sub>1-2</sub>alkoxy or hydroxy;

5           Z is:

phenyl, heteroaryl selected from pyridinyl and furanyl, heterocycle selected from 2-oxa-5-aza-bicyclo[2.2.1]heptanyl, pentamethylene sulfidyl, pentamethylene sulfoxidyl, tetrahydrofuranyl, piperazinyl, morpholino, thiomorpholino and piperidinyl,  
10 each of the aforementioned Z are optionally substituted with one to three C<sub>1-3</sub> alkyl, C<sub>1-3</sub> alkoxy, oxo, hydroxy or NH<sub>2</sub>C(O)-;

or Z is hydroxyC<sub>1-3</sub>alkyl, amino wherein the N atom is optionally independently mono- or di-substituted by pyridinylmethyl, tetrahydrofuranylmethyl, C<sub>1-3</sub> alkoxyC<sub>1-3</sub> alkyl, C<sub>1-3</sub>acyl  
15 or nitrileC<sub>1-4</sub>alkyl,  
or Z is nitrileC<sub>1-4</sub>alkyl;

R<sub>3</sub> is:

20 phenyl or heterocyclic group selected from the group consisting of pyridinyl, pyrimidinyl, and pyrazolyl, wherein such phenyl or heterocyclic group is optionally substituted with one to two groups selected from the group consisting of C<sub>1-2</sub> alkyl which is optionally partially or fully halogenated, C<sub>1-2</sub> alkoxy which optionally partially or fully halogenated, C<sub>1-2</sub>thioalkyl, C<sub>1-2</sub>thioalkylC<sub>1-3</sub>alkyl, amino or NH<sub>2</sub>C(O);

25 C<sub>1-3</sub>alkoxycarbonyl;

or R<sub>3</sub> is cyclopropyl or cyclopentyl each optionally partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl groups.

30

A still yet further preferred subgeneric aspect of the invention comprises a method of using the compounds of the formula (Ia), as described in the immediate previous paragraph, and wherein X is pyridinyl.

5

A still yet further preferred subgeneric aspect of the invention comprises a method of using the compounds of the formula (Ia), as described in the immediate previous paragraph, and wherein:

the pyridinyl is attached to Ar<sub>1</sub> via the 3-pyridinyl position.

10

The following compounds are representative of the compounds of formula(Ia) which are useful in the novel methods described herein:

15

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(4-morpholin-4-yl-methylphenyl)-naphthalen-1-yl]-urea;

20

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[3-(4-morpholin-4-yl-methylphenyl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(5-morpholin-4-yl-methylfuran-2-yl)-naphthalen-1-yl]-urea;

25

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(3-(morpholin-4-yl-methyl)cyclohexenyl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(2-(4-morpholin-4-yl)ethylphenyl)-naphthalen-1-yl]-urea;

30

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(4-dimethylaminomethylphenyl)-naphthalen-1-yl]-urea;

35

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(5-(morpholin-4-yl-methyl)pyridin-2-yl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;



1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;

5 1-[5-tert-butyl-2-methyl-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(2-(morpholin-4-yl)ethylamino)cyclohexenyl)-naphthalen-1-yl]-urea;

10 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(3,4-(morpholin-4-yl-methyl)phenyl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(4-methylpiperzin-1-yl-methyl)phenyl)-naphthalen-1-yl]-urea;

15 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(piperdin-1-yl-methyl)phenyl)-naphthalen-1-yl]-urea;

20 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(2-(pyridin-2-yl)ethylamino)cyclohexenyl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(4-(2-(pyridin-4-yl)ethylaminomethyl)phenyl)naphthalen-1-yl]-urea;

25 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(4-(pyridin-3-yl-methylaminomethyl)phenyl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(3,4-dimethoxyphenylmethyl)-3-hydroxyphenyl)naphthalen-1-yl]-urea;

30 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)naphthalen-1-yl]-urea;

35 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(morpholin-4-yl-methyl)phenyl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(morpholin-4-yl-methyl)imidazol-1-yl)naphthalen-1-yl]-urea;

40 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(4-(morpholin-4-yl-methyl)imidazol-1-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(furan-3-yl-methyl)-3-hydroxyphenyl)naphthalen-1-yl]-urea;

45 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(4-

hydroxybutylamino)pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(pyridin-3-yl-methyl)-3-hydroxyphenyl)naphthalen-1-yl]-urea;

5

1-[5-tert-butyl-2-(4-methyl-3-carbamylphenyl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

10

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(imidazol-2-yl-methyl)-3-hydroxyphenyl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(3-hydroxymorpholin-4-yl-methyl)phenyl)naphthalen-1-yl]-urea;

15

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(N-2-methoxyethyl-N-methylaminomethyl)phenyl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(4-hydroxymorpholin-4-yl-methyl)phenyl)naphthalen-1-yl]-urea;

20

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(morpholin-4-yl-methyl)cyclohexenyl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(tetrahydrofuran-3-yl-methyl)-3-hydroxyphenyl)naphthalen-1-yl]-urea;

25

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(N,N-di-(2-methoxyethyl)aminomethyl)phenyl)naphthalen-1-yl]-urea;

30

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(3-cyanopropoxy)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-morpholin-4-yl-methyl-piperidyl)naphthalen-1-yl]-urea;

35

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(N,N-di-(2-cyanoethyl)aminomethyl)phenyl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(1-morpholin-4-yl-indan-5-yl)-naphthalen-1-yl]-urea;

40

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(furan-2-yl-methyl)-3-hydroxyphenyl)naphthalen-1-yl]-urea;

45

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(thiomorpholin-4-yl-methyl)phenyl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(3-carboxamidomorpholin-4-yl-methyl)phenyl)naphthalen-1-yl]-urea;

5 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(2-methyl-3-oxo-piperzin-1-yl-methyl)phenyl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(2-methylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

10 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(4-hydroxybutyloxy)pyridin-3-yl)-naphthalen-1-yl]-urea;

15 1-[3-tert-butyl-1'H-[1,4']bipyrazol-5-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(furan-2-yl-methyl)-3-methoxyphenyl)naphthalen-1-yl]-urea;

20 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(5-(morpholin-4-carbonyl)pyrazin-2-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(tetrahydrothiopyran-4-yl-amino)pyridin-3-yl)-naphthalen-1-yl]-urea;

25 1-[5-tert-butyl-2-(2-cyanoethyl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;

30 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(2,6-dimethylmorpholin-4-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(2-methoxypyridin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;

35 1-[5-tert-butyl-2-(2-aminopyridin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-oxo-1,6-dihydropyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;

40 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-4-carbonyl)pyridin-3-yl)-naphthalen-1-yl]-urea;

45 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(4-(3-carbamylphenyl)naphthalen-1-yl)]-urea;

5 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(N-(2-cyanoethyl)-N-(pyridin-3-yl-methyl)aminomethyl)phenyl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(N-(2-cyanoethyl)-N-(pyridin-2-yl-methyl)aminomethyl)phenyl)-naphthalen-1-yl]-urea;

10 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(N-(2-cyanoethyl)-N-(tetrahydrofuran-2-yl-methyl)aminomethyl)phenyl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)-4-methoxypyridin-3-yl)-naphthalen-1-yl]-urea;

15 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(1-morpholin-4-yl-propyl)pyridin-3-yl)-naphthalen-1-yl]-urea;

20 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(N-(3-methoxypropyl)amino)pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(N-(3-methoxypropyl)-N-methylamino)pyridin-3-yl)-naphthalen-1-yl]-urea;

25 1-[3-tert-butyl-1'-methyl-1'H-[1,4']bipyrazol-5-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-benzyl-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;

30 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(N-N-di-(2-cyanoethyl)aminomethyl)phenyl)-naphthalen-1-yl]-urea;

35 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(4-(4-carbamylphenyl)naphthalen-1-yl)]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(1-oxo-tetrahydrothiopyran-4-yl-amino)pyridin-3-yl)-naphthalen-1-yl]-urea;

40 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(tetrahydropyran-4-yl-amino)pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[3-tert-butyl-1'-(3-cyanopropyl)-1'H-[1,4']bipyrazol-5-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

45 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(3-methanesulfinylphenyl)naphthalen-1-

yl]-urea;

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(3-methanesulfonylphenyl)naphthalen-1-yl]-urea;

5

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(3-sulfonamidophenyl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(3-(morpholin-4-yl)carbonylphenyl)naphthalen-1-yl]-urea;

10

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(5-(tetrahydrothiopyran-4-yl-amino)pyrazin-2-yl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(methylcarbonylamino)pyridin-3-yl)-naphthalen-1-yl]-urea;

15

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-4-carbonyl)phenyl)-naphthalen-1-yl]-urea;

20

1-[3-tert-butyl-1'-(3-methylsulfanylpropyl)-1'H-[1,4']bipyrazol-5-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(5-(morpholin-4-yl-carbonyl)pyridin-3-yl)-naphthalen-1-yl]-urea;

25

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(5-(morpholin-4-yl-methyl)pyrazin-2-yl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-aminopyridin-3-yl)naphthalen-1-yl]-urea;

30

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(1-methylpiperdin-4-yl-amino)pyridin-3-yl)naphthalen-1-yl]-urea;

35

1-[5-tert-butyl-2-(2-methylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(2-methyl-3-oxo-piperzin-1-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(2-methylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-carbonyl)pyridin-3-yl)naphthalen-1-yl]-urea;

40

1-[5-tert-butyl-2-(2-methylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(N,N-di-(2-methoxyethyl)aminomethyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(2-methylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(1-oxo-thiomorpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

45

1-[5-tert-butyl-2-(2-methylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(tetrahydropyran-4-yl-amino)pyridin-3-yl)naphthalen-1-yl]-urea;

5 1-[5-tert-butyl-2-(2-methylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(5-(morpholin-4-yl-methyl)pyrazin-2-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(2-methylthiopyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

10 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(2-methyl-3-oxo-piperzin-1-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(pyridin-3-yl-oxy)pyridin-3-yl)naphthalen-1-yl]-urea

15 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(pyridin-3-yl-amino)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(2-methoxypyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(5-carbamylpyridin-3-yl)naphthalen-1-yl]-urea;

25 1-[5-tert-butyl-2-(2-aminopyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(2-methylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(4-(morpholin-4-yl-methyl)phenyl)naphthalen-1-yl]-urea;

30 1-[3-tert-butyl-1'-methyl-1'H-[1,4']bipyrazol-5-yl]-3-[4-(6-(morpholin-4-yl-methyl)phenyl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(2-cyclopropylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(2-(pyridin-3-yl-amino)pyrimidin-5-yl)naphthalen-1-yl]-urea;

40 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(1-oxo-tetrahydrothiopyran-4-yl-amino)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(thiomorpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

45 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(3-benzyl-3H-imidazo[4,5-b]pyridin-6-

yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(pyridin-3-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

5

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(2-(morpholin-4-yl-carbonyl)pyrimidin-5-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(2-(morpholin-4-yl-methyl)pyrimidin-5-yl)naphthalen-1-yl]-urea;

10

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(3-amino-4-carbamylphenyl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(1-oxo-thiomorpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

15

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(pyridin-3-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

20

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(hydroxy-pyridin-3-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(2-methylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(2-(morpholin-4-yl-methyl)pyrimidin-5-yl)naphthalen-1-yl]-urea;

25

and the pharmaceutically acceptable derivatives thereof.

30

In another embodiment of the invention there are provided the following compounds of formula(Ia) which are useful in the novel methods described herein:

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1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(5-(morpholin-4-yl-methyl)pyridin-2-yl)naphthalen-1-yl]-urea;

40

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(2-(pyridin-2-yl)ethylamino)cyclohexenyl)naphthalen-1-yl]-urea;

45

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(4-(pyridin-3-yl-methylaminomethyl)phenyl)naphthalen-1-yl]-urea;

5 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(morpholin-4-yl-methyl)phenyl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(4-hydroxybutylamino)pyridin-3-yl)-naphthalen-1-yl]-urea;

10 1-[5-tert-butyl-2-(4-methyl-3-carbamylphenyl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

15 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(3-hydroxypiperidin-1-yl-methyl)phenyl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(4-hydroxymorpholin-4-yl-methyl)phenyl)naphthalen-1-yl]-urea;

20 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(morpholin-4-yl-methyl)cyclohexenyl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(tetrahydrofuran-3-yl-methyl)-3-hydroxyphenyl)naphthalen-1-yl]-urea;

25 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(N,N-di-(2-methoxyethyl)aminomethyl)phenyl)naphthalen-1-yl]-urea;

30 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(3-cyanopropoxy)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-morpholin-4-yl-methyl-piperidinyl)naphthalen-1-yl]-urea;

35 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(N,N-di-(2-cyanoethyl)aminomethyl)phenyl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(furan-2-yl-methyl)-3-hydroxyphenyl)naphthalen-1-yl]-urea;

40 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(thiomorpholin-4-yl-methyl)phenyl)naphthalen-1-yl]-urea;

45 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(3-carboxamidopiperidin-1-yl-methyl)phenyl)naphthalen-1-yl]-urea;



1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(2-methyl-3-oxo-piperzin-1-yl-methyl)phenyl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(2-methylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(4-hydroxybutyloxy)pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[3-tert-butyl-1'H-[1,4']bipyrazol-5-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(tetrahydrothiopyran-4-yl-amino)pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(2-cyanoethyl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(2,6-dimethylmorpholin-4-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(2-methoxypyridin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(2-aminopyridin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-4-carbonyl)pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(N-(2-cyanoethyl)-N-(pyridin-3-yl-methyl)aminomethyl)phenyl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(N-(2-cyanoethyl)-N-(tetrahydrofuran-2-yl-methyl)aminomethyl)phenyl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)-4-methoxypyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(1-morpholin-4-yl-propyl)pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[3-tert-butyl-1'-methyl-1'H-[1,4']bipyrazol-5-yl]-3-[4-(6-(morpholin-4-yl-

methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(1-oxo-tetrahydrothiopyran-4-yl-amino)pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(tetrahydropyran-4-yl-amino)pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(5-(tetrahydrothiopyran-4-yl-amino)pyrazin-2-yl)-naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(methylcarbonylamino)pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[3-tert-butyl-1'-(3-methylsulfanylpropyl)-1'H-[1,4']bipyrazol-5-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(2-methylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(1-oxo-thiomorpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(2-methylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(tetrahydropyran-4-yl-amino)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(2-methylthiopyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(2-aminopyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[3-tert-butyl-1'-methyl-1'H-[1,4']bipyrazol-5-yl]-3-[4-(6-(morpholin-4-yl-methyl)phenyl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(1-oxo-tetrahydrothiopyran-4-yl-amino)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(thiomorpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(2-(morpholin-4-yl-carbonyl)pyrimidin-5-yl)naphthalen-1-yl]-urea;

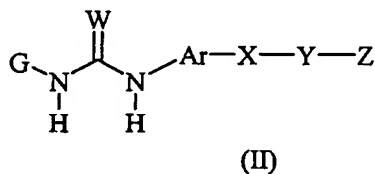
1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(2-(morpholin-4-yl-methyl)pyrimidin-5-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(1-oxo-thiomorpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

1-[5-tert-butyl-2-(2-methylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(2-(morpholin-4-yl-methyl)pyrimidin-5-yl)naphthalen-1-yl]-urea and

5 the pharmaceutically acceptable derivatives thereof.

10 In a third broad generic aspect, there is provided a method of treating a cytokine mediated disease or condition chosen from: acute and chronic inflammation in the lung caused by inhalation of smoke, endometriosis, Behcet's disease, uveitis, ankylosing spondylitis, pancreatitis, cancer, Lyme disease, restenosis following percutaneous transluminal coronary angioplasty, Alzheimer's disease, traumatic arthritis, sepsis, chronic obstructive  
15 pulmonary disease and congestive heart failure, said method comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of the formula (II) disclosed in WO 00/55139 which is the PCT case of US application serial no. 09/505,582:



wherein:

G is :

30 an aromatic C<sub>6-10</sub> carbocycle or a nonaromatic C<sub>3-10</sub> carbocycle saturated or unsaturated;

a 6-10 membered heteroaryl containing 1 or more heteroatoms chosen from O, N and S;

a 5-8 membered monocyclic heterocycle containing one or more heteroatoms chosen from O, N and S;

or

an 8-11 membered bicyclic heterocycle, containing one or more heteroatoms chosen from O, N and S;

wherein G is substituted by one or more R<sub>1</sub>, R<sub>2</sub> or R<sub>3</sub>;

Ar is:

phenyl, naphthyl, quinolinyl, isoquinolinyl, tetrahydronaphthyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, benzimidazolyl, benzofuranyl, dihydrobenzofuranyl, indolyl, benzothienyl, dihydrobenzothienyl, indanyl, indenyl or indolyl each being optionally substituted by one or more R<sub>4</sub> or R<sub>5</sub>;

X is:

a C<sub>5-8</sub> cycloalkyl or cycloalkenyl optionally substituted with one to two oxo groups or one to three C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy or C<sub>1-4</sub> alkylamino chains;

phenyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyridinonyl, dihydropyridinonyl, maleimidyl, dihydromaleimidyl, piperdinyl, benzimidazole, 3H-imidazo[4,5-b]pyridine, piperazinyl, pyridazinyl or pyrazinyl;

Y is:

a bond or a C<sub>1-4</sub> saturated or unsaturated branched or unbranched carbon chain optionally partially or fully halogenated, wherein one or more methylene groups are optionally replaced by O, N, or S(O)<sub>m</sub> and wherein Y is optionally independently substituted with

one to two oxo groups, phenyl or one or more C<sub>1-4</sub> alkyl optionally substituted by one or more halogen atoms;

Z is:

5

phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, pyranyl each being optionally substituted with one to three halogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, hydroxy, amino, mono- or di-(C<sub>1-3</sub> alkyl)amino, C<sub>1-6</sub> alkyl-S(O)<sub>m</sub>, CN, CONH<sub>2</sub>, COOH or phenylamino wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy;

10

tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxolanonyl, 1,3-dioxanonyl, 1,4-dioxanyl, morpholinyl, thiomorpholinyl, thiomorpholino sulfoxidyl, thiomorpholino sulfonyl, piperidinyl, piperidinonyl, piperazinyl, tetrahydropyrimidinonyl, cyclohexanonyl, cyclohexanolyl, pentamethylene sulfidyl, pentamethylene sulfoxidyl, pentamethylene sulfonyl, tetramethylene sulfide, tetramethylene sulfoxidyl or tetramethylene sulfonyl each being optionally substituted with one to three nitrile, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, hydroxy, amino, mono- or di-(C<sub>1-3</sub> alkyl)amino-C<sub>1-3</sub> alkyl, CONH<sub>2</sub>, phenylamino-C<sub>1-3</sub> alkyl or C<sub>1-3</sub> alkoxy-C<sub>1-3</sub> alkyl;

15

20

halogen, C<sub>1-4</sub> alkyl, nitrile, amino, hydroxy, C<sub>1-6</sub> alkoxy, NH<sub>2</sub>C(O), mono- or di-(C<sub>1-3</sub>alkyl) aminocarbonyl, mono- or di-(C<sub>1-6</sub>alkyl)amino, secondary or tertiary amine wherein the amino nitrogen is covalently bonded to C<sub>1-3</sub> alkyl or C<sub>1-5</sub> alkoxyalkyl, pyridinyl-C<sub>1-3</sub> alkyl, imidazolyl-C<sub>1-3</sub> alkyl, tetrahydrofuranyl-C<sub>1-3</sub> alkyl, nitrile-C<sub>1-3</sub> alkyl, carboxamide-C<sub>1-3</sub> alkyl, phenyl, wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkoxy, hydroxy or mono- or di-(C<sub>1-3</sub> alkyl)amino, C<sub>1-6</sub> alkyl-S(O)<sub>m</sub>, or phenyl-S(O)<sub>m</sub>, wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkoxy, hydroxy, halogen or mono- or di-(C<sub>1-3</sub> alkyl)amino;

25

30

C<sub>1-6</sub> alkyl-S(O)<sub>m</sub>, and phenyl-S(O)<sub>m</sub>, wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkoxy, hydroxy or mono- or di-(C<sub>1-3</sub> alkyl)amino;

each R<sub>1</sub> is independently:

C<sub>1-10</sub> alkyl optionally be partially or fully halogenated, and optionally substituted with  
5 one to three C<sub>3-10</sub> cycloalkanyl, hydroxy, phenyl, naphthyl, pyridinyl, pyrimidinyl,  
pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl or  
isothiazolyl; each of the aforementioned being optionally substituted with one to five  
groups selected from halogen, C<sub>1-6</sub> alkyl which is optionally partially or fully  
halogenated, C<sub>3-8</sub> cycloalkanyl, C<sub>5-8</sub> cycloalkenyl, hydroxy, nitrile, C<sub>1-3</sub> alkoxy which is  
10 optionally partially or fully halogenated or NH<sub>2</sub>C(O), mono- or di(C<sub>1-3</sub>alkyl)amino, and  
mono- or di(C<sub>1-3</sub>alkyl)aminocarbonyl;

cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, or cycloheptyloxy each  
being optionally partially or fully halogenated and optionally substituted with one to three  
15 C<sub>1-3</sub> alkyl groups optionally partially or fully halogenated, CN, hydroxyC<sub>1-3</sub>alkyl or aryl;  
or an analog of such cycloalkyl group wherein one to three ring methylene groups are  
independently replaced by O, S(O)<sub>m</sub>, CHOH, >C=O, >C=S or NH;

phenyloxy or benzyloxy each being optionally partially or fully halogenated and  
20 optionally substituted with one to three C<sub>1-3</sub> alkyl groups optionally partially or fully  
halogenated, CN, hydroxyC<sub>1-3</sub>alkyl or aryl; or an analog of such cycloaryl group wherein  
one to two ring methyne groups are independently replaced by N;

cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl,  
25 bicyclopentanyl, bicyclohexanyl or bicycloheptanyl, each being optionally partially or  
fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl groups optionally  
partially or fully halogenated, CN, hydroxyC<sub>1-3</sub>alkyl or aryl; or an analog of such  
cycloalkyl group wherein one to three ring methylene groups are independently replaced  
by O, S(O)<sub>m</sub>, CHOH, >C=O, >C=S or NH;

30

C<sub>3-10</sub> branched or unbranched alkenyl each being optionally partially or fully halogenated, and optionally be substituted with one to three C<sub>1-5</sub> branched or unbranched alkyl, phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl or isothiazolyl, each of the aforementioned being substituted  
5 with zero to five halogen, C<sub>1-6</sub> alkyl which is optionally partially or fully halogenated, cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, hydroxy, nitrile, C<sub>1-3</sub> alkyloxy which is optionally partially or fully halogenated, NH<sub>2</sub>C(O), mono- or di(C<sub>1-3</sub>alkyl)aminocarbonyl; the C<sub>3-10</sub> branched or unbranched alkenyl being optionally  
10 interrupted by one or more heteroatoms chosen from O, N and S(O)<sub>m</sub>;

cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl or bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C<sub>1-3</sub> alkyl groups;

15 nitrile, halogen;

methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl;

20 silyl containing three C<sub>1-4</sub> alkyl groups optionally partially or fully halogenated;

C<sub>3-6</sub> alkynyl branched or unbranched carbon chain optionally partially or fully halogenated, wherein one or more methylene groups are optionally replaced by O, NH or S(O)<sub>m</sub> and wherein said alkynyl group is optionally independently substituted with one to  
25 two oxo groups, pyrrolidinyl, pyrrolyl, one or more C<sub>1-4</sub> alkyl optionally substituted by one or more halogen atoms, nitrile, morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl, or mono- or di(C<sub>1-3</sub>alkyl)amino optionally substituted by one or more halogen atoms;

30 each R<sub>2</sub>, R<sub>4</sub>, and R<sub>5</sub> is

a C<sub>1-6</sub> branched or unbranched alkyl optionally partially or fully halogenated, acetyl, aroyl, C<sub>1-4</sub> branched or unbranched alkoxy, each being optionally partially or fully halogenated, halogen, nitrile, methoxycarbonyl, C<sub>1-3</sub> alkyl-S(O)<sub>m</sub> optionally partially or fully halogenated, or phenylsulfonyl;

5

C<sub>1-6</sub> alkoxy, hydroxy, amino, or mono- or di-(C<sub>1-4</sub> alkyl)amino, nitrile, halogen;

OR<sub>6</sub>;

10    nitro; or

mono- or di-(C<sub>1-4</sub> alkyl)amino-S(O)<sub>2</sub> optionally partially or fully halogenated, or H<sub>2</sub>NSO<sub>2</sub>;

15           each R<sub>3</sub> is independently:

phenyl, naphthyl, morpholinyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrrolidinyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, triazolyl, tetrazolyl, thienyl, furyl, tetrahydrofuryl, isoxazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl, quinoxalinyl, quinazolinyl, purinyl or indazolyl, each of the aforementioned is optionally substituted with one to three phenyl, naphthyl, heterocycle or heteroaryl as hereinabove described in this paragraph, C<sub>1-6</sub> branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclopentyl, bicyclohexyl, bicycloheptyl, phenyl C<sub>1-5</sub> alkyl, naphthyl C<sub>1-5</sub> alkyl, halogen, hydroxy, oxo, nitrile, C<sub>1-3</sub> alkyloxy optionally partially or fully halogenated, phenyloxy, naphthyloxy, heteroaryloxy or heterocycloxy wherein the heterocyclic or heteroaryl moiety is as hereinabove described in this paragraph, nitro, amino, mono- or di-(C<sub>1-3</sub>alkyl)amino, phenylamino, naphthylamino, heteroaryl or heterocyclic amino wherein the heteroaryl heterocyclic moiety is as hereinabove described in this paragraph,

25  
30



NH<sub>2</sub>C(O), a mono- or di-(C<sub>1-3</sub>alkyl) aminocarbonyl, C<sub>1-5</sub> alkyl-C(O)-C<sub>1-4</sub> alkyl, amino-C<sub>1-5</sub> alkyl, mono- or di-(C<sub>1-3</sub>alkyl)amino-C<sub>1-5</sub> alkyl, amino-S(O)<sub>2</sub>, di-(C<sub>1-3</sub>alkyl)amino-S(O)<sub>2</sub>, R<sub>7</sub>-C<sub>1-5</sub> alkyl, R<sub>8</sub>-C<sub>1-5</sub> alkoxy, R<sub>9</sub>-C(O)-C<sub>1-5</sub> alkyl, R<sub>10</sub>-C<sub>1-5</sub> alkyl(R<sub>11</sub>)N, carboxy-mono- or di-(C<sub>1-5</sub>alkyl)-amino;

5

a fused aryl selected from benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl, or a fused heteroaryl selected from cyclopentenopyridinyl, cyclohexanopyridinyl, cyclopentanopyrimidinyl, cyclohexanopyrimidinyl, cyclopentanopyrazinyl, cyclohexanopyrazinyl, cyclopentanopyridazinyl, cyclohexanopyridazinyl, cyclopentanoquinolinyl, cyclohexanoquinolinyl, cyclopentanoisoquinolinyl, cyclohexanoisoquinolinyl, cyclopentanoindolyl, cyclohexanoindolyl, cyclopentanobenzimidazolyl, cyclohexanobenzimidazolyl, cyclopentanobenzoxazolyl, cyclohexanobenzoxazolyl, cyclopentanoimidazolyl, cyclohexanoimidazolyl, cyclopentanthienyl and cyclohexanthienyl; wherein the fused aryl or fused heteroaryl ring is independently substituted with zero to three phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, isothiazolyl, C<sub>1-6</sub> alkyl which is optionally partially or fully halogenated, halogen, nitrile, C<sub>1-3</sub> alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heteroaryloxy or heterocycloxy wherein the heteroaryl or heterocyclic moiety is as hereinabove described in this paragraph, nitro, amino, mono- or di-(C<sub>1-3</sub>alkyl)amino, phenylamino, naphthylamino, heteroaryl or heterocyclic amino wherein the heteroaryl or heterocyclic moiety is as hereinabove described in this paragraph, NH<sub>2</sub>C(O), mono- or di-(C<sub>1-3</sub>alkyl)aminocarbonyl, C<sub>1-4</sub> alkyl-OC(O), C<sub>1-5</sub> alkyl-C(O)-C<sub>1-4</sub> alkyl, amino-C<sub>1-5</sub> alkyl, mono- or di-(C<sub>1-3</sub>)alkylamino-C<sub>1-5</sub> alkyl, R<sub>12</sub>-C<sub>1-5</sub> alkyl, R<sub>13</sub>-C<sub>1-5</sub> alkoxy, R<sub>14</sub>-C(O)-C<sub>1-5</sub> alkyl or R<sub>15</sub>-C<sub>1-5</sub> alkyl(R<sub>16</sub>)N;

30

cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl or bicycloheptanyl, each being optionally partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl groups, or an

analog of such cycloalkyl group wherein one to three ring methylene groups are independently replaced by O, S, CHOH,  $>C=O$ ,  $>C=S$  or NH;

cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl,

5 bicyclohexenyl or bicycloheptenyl, each optionally substituted with one to three  $C_{1-3}$  alkyl groups;

$C_{1-4}$  alkyl-phenyl- $C(O)-C_{1-4}$  alkyl-,  $C_{1-4}$  alkyl- $C(O)-C_{1-4}$  alkyl- or  $C_{1-4}$  alkyl-phenyl- $S(O)_m-C_{1-4}$  alkyl-;

10

$C_{1-6}$  alkyl or  $C_{1-6}$  branched or unbranched alkoxy each of which is optionally partially or fully halogenated or optionally substituted with  $R_{17}$ ;

$OR_{18}$  or  $C_{1-6}$  alkyl optionally substituted with  $OR_{18}$ ;

15

amino or mono- or di- $(C_{1-5}$ alkyl)amino optionally substituted with  $R_{19}$ ;

$R_{20}C(O)N(R_{21})-$ ,  $R_{22}O-$  or  $R_{23}R_{24}NC(O)-$ ;  $R_{26}(CH_2)_mC(O)N(R_{21})-$  or  $R_{26}C(O)(CH_2)_mN(R_{21})-$ ;

20

$C_{2-6}$ alkenyl substituted by  $R_{23}R_{24}NC(O)-$ ;

$C_{2-6}$  alkynyl branched or unbranched carbon chain, optionally partially or fully

halogenated, wherein one or more methylene groups are optionally replaced by O, NH,

25  $S(O)_m$  and wherein said alkynyl group is optionally independently substituted with one to

two oxo groups, pyrrolidinyl, pyrrolyl, morpholinyl, piperidinyl, piperazinyl, imidazolyl,

phenyl, pyridinyl, tetrazolyl one or more  $C_{1-4}$  alkyl optionally substituted by one or more

halogen atoms, nitrile, morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl,

pyridinyl, tetrazolyl, or mono- or di- $(C_{1-4}$  alkyl)amino optionally substituted by one or

30

more halogen atoms; or

aroyl;

R<sub>6</sub> is a:

5 C<sub>1-4</sub> alkyl optionally partially or fully halogenated and optionally substituted with R<sub>26</sub>;

each R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, R<sub>12</sub>, R<sub>13</sub>, R<sub>14</sub>, R<sub>15</sub>, R<sub>17</sub>, R<sub>19</sub>, R<sub>25</sub> and R<sub>26</sub> is independently:  
nitrile, phenyl, morpholino, piperidinyl, piperazinyl, imidazolyl, pyridinyl, tetrazolyl,  
amino or mono- or di-(C<sub>1-4</sub>alkyl)amino optionally partially or fully halogenated;

10

each R<sub>11</sub> and R<sub>16</sub> is independently:  
hydrogen or C<sub>1-4</sub> alkyl optionally partially or fully halogenated;

R<sub>18</sub> is independently:

15 hydrogen or a C<sub>1-4</sub> alkyl optionally independently substituted with oxo or R<sub>25</sub>;

R<sub>20</sub> is independently:

C<sub>1-10</sub> alkyl optionally partially or fully halogenated, phenyl, or pyridinyl;

20

R<sub>21</sub> is independently:  
hydrogen or C<sub>1-3</sub> alkyl optionally partially or fully halogenated;

each R<sub>22</sub>, R<sub>23</sub> and R<sub>24</sub> is independently:

hydrogen, C<sub>1-6</sub> alkyl optionally partially or fully halogenated, said C<sub>1-6</sub> alkyl is optionally  
25 interrupted by one or more O, N or S, said C<sub>1-6</sub> alkyl also being independently optionally  
substituted by mono- or di-(C<sub>1-3</sub>alkyl)aminocarbonyl, phenyl, pyridinyl, amino or mono-  
or di-(C<sub>1-4</sub>alkyl)amino each of which is optionally partially or fully halogenated and  
optionally substituted with mono- or di-(C<sub>1-3</sub>alkyl)amino;  
or R<sub>23</sub> and R<sub>24</sub> taken together optionally form a heterocyclic or heteroaryl ring;

30

m = 0, 1 or 2;

W is O or S and

the pharmaceutically acceptable derivatives thereof.

5

A preferred subgeneric aspect of the invention comprises a method of using the compounds of the formula(II) as provided above and wherein:

10 G is:

phenyl, naphthyl, benzocyclobutanyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl, benzocycloheptenyl, indanyl, indenyl;

pyridinyl, pyridonyl, quinolinyl, dihydroquinolinyl, tetrahydroquinoyl, isoquinolinyl,  
15 tetrahydroisoquinoyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, benzofuranyl, benzothiophenyl, benzpyrazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, benzooxazolonyl, benzo[1,4]oxazin-3-onyl, benzodioxolyl, benzo[1,3]dioxol-2-onyl, benzofuran-3-onyl, tetrahydrobenzopyranyl, indolyl, indolinyl, indolonyl, indolinonyl, phthalimidyl;

20 oxetanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, dioxanyl, tetramethylene sulfonyl, tetramethylene sulfoxidyl, oxazoliny, thiazoliny, imidazoliny, tetrahydropyridiny, homopiperidinyl, pyrroliny, tetrahydropyrimidinyl, decahydroquinolinyl, decahydroisoquinolinyl, thiomorpholinyl, thiazolidinyl, dihydrooxazinyl, dihydropyranyl, oxocanyl, heptacanyl,  
25 thioxanyl or dithianyl;

wherein G is substituted by one or more R<sub>1</sub>, R<sub>2</sub> or R<sub>3</sub>;

30 A more preferred subgeneric aspect of the invention comprises a method of using the compounds of the formula(II) as provided above and wherein:

G is phenyl, pyridinyl, pyridonyl, naphthyl, quinolinyl, isoquinolinyl, pyrazinyl, benzimidazolyl, benzoxazolyl, benzofuranyl, benzothiophenyl, benzpyrazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, indanyl, indenyl, indolyl, indolinyl, indolonolyl or indolinonyl, wherein G is substituted by one or more R<sub>1</sub>, R<sub>2</sub> or R<sub>3</sub>;

Ar is:

naphthyl, quinolinyl, isoquinolinyl, tetrahydronaphthyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, indanyl, indenyl or indolyl each being optionally substituted by one or more R<sub>4</sub> or R<sub>5</sub> groups;

X is:

phenyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyridinonyl, dihydropyridinonyl, maleimidyl, dihydromaleimidyl, piperdiny, piperazinyl, pyridazinyl or pyrazinyl

Y is:

a bond or

a C<sub>1-4</sub> saturated or unsaturated carbon chain wherein one of the carbon atoms is optionally replaced by O, N, or S(O)<sub>m</sub> and wherein Y is optionally independently substituted with one to two oxo groups, phenyl or one or more C<sub>1-4</sub> alkyl optionally substituted by one or more halogen atoms;

Z is:

phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, furanyl, thienyl, dihydrothiazolyl, dihydrothiazolyl sulfoxidyl, pyranyl, pyrrolidinyl which are optionally

substituted with one to three nitrile, C<sub>1-3</sub> alkyl, C<sub>1-3</sub> alkoxy, amino, mono- or di-(C<sub>1-3</sub> alkyl)amino, CONH<sub>2</sub> or OH;

5 tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxolanonyl, 1,3-dioxanonyl, 1,4-dioxanyl, morpholinyl, thiomorpholinyl, thiomorpholino sulfoxidyl, piperidinyl, piperidinonyl, piperazinyl, tetrahydropyrimidonyl, pentamethylene sulfidyl, pentamethylene sulfoxidyl, pentamethylene sulfonyl, tetramethylene sulfidyl, tetramethylene sulfoxidyl or tetramethylene sulfonyl which are optionally substituted with one to three nitrile, C<sub>1-3</sub> alkyl, C<sub>1-3</sub> alkoxy, amino, mono- or di-(C<sub>1-3</sub> alkyl)amino, CONH<sub>2</sub>, or OH;  
10 nitrile, C<sub>1-6</sub> alkyl-S(O)<sub>m</sub>, halogen, hydroxy, C<sub>1-4</sub> alkoxy, amino, mono- or di-(C<sub>1-6</sub> alkyl)amino, mono- or di-(C<sub>1-3</sub> alkyl)aminocarbonyl or NH<sub>2</sub>C(O);

each R<sub>1</sub> is independently:

15 C<sub>3-6</sub> alkyl optionally partially or fully halogenated, and optionally substituted with one to three C<sub>3-6</sub>cycloalkyl, phenyl, thienyl, furyl, isoxazolyl or isothiazolyl; each of the aforementioned being optionally substituted with one to three groups selected from halogen, C<sub>1-3</sub> alkyl which is optionally partially or fully halogenated, hydroxy, nitrile or C<sub>1-3</sub>alkoxy which is optionally partially or fully halogenated;

20 cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, bicyclopentanyl or bicyclohexanyl, each being optionally partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl groups optionally partially or fully halogenated, CN, hydroxyC<sub>1-3</sub>alkyl or phenyl; or an analog of such cycloalkyl group wherein one to three ring methylene  
25 groups are independently replaced by O, S, CHOH, >C=O, >C=S or NH; or

silyl containing three C<sub>1-4</sub> alkyl groups optionally partially or fully halogenated;

R<sub>2</sub> is independently:

halogen, C<sub>1-3</sub> alkoxy, C<sub>1-3</sub> alkyl-S(O)<sub>m</sub> optionally partially or fully halogenated, phenylsulfonyl or nitrile;

5

R<sub>3</sub> is independently:

phenyl, morpholino, pyridinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrrolylidinyl, imidazolyl, pyrazolyl, each being optionally substituted with one to three phenyl,  
 10 naphthyl, heterocycle or heteroaryl as hereinabove described in this paragraph, C<sub>1-6</sub> alkyl which is optionally partially or fully halogenated, cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C<sub>1-5</sub> alkyl, naphthyl C<sub>1-5</sub> alkyl, halogen, oxo, hydroxy, nitrile, C<sub>1-3</sub> alkyloxy optionally partially or fully halogenated, phenyloxy, naphthyloxy, heteroaryloxy  
 15 or heterocycloxy wherein the heteroaryl or heterocyclic moiety is as hereinabove described in this paragraph, nitro, amino, mono- or di-(C<sub>1-3</sub>alkyl)amino, phenylamino, naphthylamino, heteroaryl or heterocyclic amino wherein the heteroaryl or heterocyclic moiety is as hereinabove described in this paragraph, NH<sub>2</sub>C(O), a mono- or di-(C<sub>1-3</sub>alkyl)aminocarbonyl, C<sub>1-5</sub> alkyl-C(O)-C<sub>1-4</sub> alkyl, mono- or di-(C<sub>1-3</sub>alkyl)amino, mono- or  
 20 di-(C<sub>1-3</sub>alkylamino)-C<sub>1-5</sub> alkyl, mono- or di-(C<sub>1-3</sub>alkyl)amino-S(O)<sub>2</sub>, R<sub>7</sub>-C<sub>1-5</sub> alkyl, R<sub>8</sub>-C<sub>1-5</sub> alkoxy, R<sub>9</sub>-C(O)-C<sub>1-5</sub> alkyl, R<sub>10</sub>-C<sub>1-5</sub> alkyl(R<sub>11</sub>)N, carboxy-mono- or di-(C<sub>1-5</sub>)-alkyl-amino;

C<sub>1-3</sub> alkyl or C<sub>1-4</sub> alkoxy each being optionally partially or fully halogenated or optionally  
 25 substituted with R<sub>17</sub>;

OR<sub>18</sub> or C<sub>1-6</sub> alkyl optionally substituted with OR<sub>18</sub>;

amino or mono- or di- (C<sub>1-5</sub> alkyl)amino optionally substituted with R<sub>19</sub>;

30

R<sub>20</sub>C(O)N(R<sub>21</sub>)-, R<sub>22</sub>O-; R<sub>23</sub>R<sub>24</sub>NC(O)-; R<sub>26</sub>CH<sub>2</sub>C(O)N(R<sub>21</sub>)- or R<sub>26</sub>C(O)CH<sub>2</sub>N(R<sub>21</sub>)-;

C<sub>2-4</sub>alkenyl substituted by R<sub>23</sub>R<sub>24</sub>NC(O)-; or

C<sub>2-4</sub> alkynyl branched or unbranched carbon chain optionally partially or fully halogenated and optionally independently substituted with one to two oxo groups,  
5 pyrroldinyl, pyrrolyl, morpholinyl, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl or one or more C<sub>1-4</sub> alkyl optionally substituted by one or more halogen atoms; and  
R<sub>23</sub> and R<sub>24</sub> taken together optionally form imidazolyl, piperidinyl, morpholinyl, piperazinyl or a pyridinyl ring.

10

A yet more preferred subgeneric aspect of the invention comprises a method of using the compounds of the formula (II), as described in the immediate previous paragraph, wherein:

15

G is phenyl, pyridinyl, pyridonyl, naphthyl, quinolinyl, isoquinolinyl, pyrazinyl, benzothiophenyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, indanyl, indolyl,  
20 indolinyl, indolonyl or indolinonyl, wherein G is substituted by one or more R<sub>1</sub>, R<sub>2</sub> or R<sub>3</sub>;

Ar is naphthyl;

25

X is  
phenyl, imidazolyl, pyridinyl, pyrimidinyl, piperdinyl, piperazinyl, pyridazinyl or pyrazinyl each being optionally independently substituted with one to three C<sub>1-4</sub> alkyl, C<sub>1-4</sub>alkoxy, hydroxy, nitrile, amino, mono- or di-(C<sub>1-3</sub> alkyl)amino, mono- or di-(C<sub>1-3</sub> alkylamino)carbonyl, NH<sub>2</sub>C(O), C<sub>1-6</sub> alkyl-S(O)<sub>m</sub> or halogen;

30

Y is:  
a bond or



a C<sub>1-4</sub> saturated carbon chain wherein one of the carbon atoms is optionally replaced by O, N or S and wherein Y is optionally independently substituted with an oxo group;

Z is:

5

phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, dihydrothiazolyl, dihydrothiazolyl sulfoxide, pyranyl or pyrrolidinyl which are optionally substituted with one to two C<sub>1-2</sub> alkyl or C<sub>1-2</sub> alkoxy;

10

tetrahydropyranyl, morpholinyl, thiomorpholinyl, thiomorpholino sulfoxidyl, piperidinyl, piperidinonyl, piperazinyl or tetrahydropyrimidinonyl which are optionally substituted with one to two C<sub>1-2</sub> alkyl or C<sub>1-2</sub> alkoxy; or

C<sub>1-3</sub> alkoxy;

15

each R<sub>1</sub> is independently:

C<sub>3-5</sub> alkyl optionally partially or fully halogenated, and optionally substituted with phenyl substituted with zero to three halogen, C<sub>1-3</sub> alkyl which is optionally partially or fully halogenated, hydroxy, nitrile or C<sub>1-3</sub>alkoxy which is optionally partially or fully halogenated;

25

cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, bicyclopentanyl or bicyclohexanyl, each being optionally partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl groups optionally partially or fully halogenated, CN, hydroxyC<sub>1-3</sub>alkyl or phenyl; and an analog of cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, bicyclopentanyl or bicyclohexanyl wherein one ring methylene group is replaced by O; and

30

silyl containing three C<sub>1-2</sub> independently alkyl groups optionally partially or fully halogenated;

each  $R_2$  is independently:

bromo, chloro, fluoro, methoxy, methylsulfonyl or nitrile;

5

each  $R_3$  is independently:

phenyl, morpholino, pyridinyl, pyrimidinyl, pyrrolidinyl, 2,5-pyrrolidin-dionyl,

10 imidazolyl, pyrazolyl, each of the aforementioned is optionally substituted with one to three  $C_{1-3}$  alkyl which is optionally partially or fully halogenated, halogen, oxo, hydroxy, nitrile and  $C_{1-3}$  alkyloxy optionally partially or fully halogenated;

$C_{1-3}$  alkyl or  $C_{1-3}$  alkoxy each being optionally partially or fully halogenated or optionally  
15 substituted with  $R_{17}$ ;

$OR_{18}$  or  $C_{1-3}$  alkyl optionally substituted with  $OR_{18}$ ;

amino or mono- or di- $(C_{1-3}$  alkyl)amino optionally substituted with  $R_{19}$ ;

20  $R_{20}C(O)N(R_{21})-$ ,  $R_{22}O-$ ;  $R_{23}R_{24}NC(O)-$ ;  $R_{26}CH_2C(O)N(R_{21})-$  or  $R_{26}C(O)CH_2N(R_{21})-$ ;

$C_{2-4}$  alkenyl substituted by  $R_{23}R_{24}NC(O)-$ ; or

$C_{2-4}$  alkynyl substituted with pyrrolidinyl or pyrrolyl;

25 and

$R_{23}$  and  $R_{24}$  taken together optionally form morpholino.

30 A yet further preferred subgeneric aspect of the invention comprises a method of using the compounds of the formula (II), as described in the immediate previous paragraph, and wherein:

G is phenyl, pyridinyl, pyridonyl, naphthyl, quinoliny, isoquinoliny,  
5 dihydrobenzofuranyl, indanyl, indoliny, indolonyl, or indolinonyl, wherein G is  
substituted by one or more R<sub>1</sub>, R<sub>2</sub> or R<sub>3</sub>;

Ar is 1-naphthyl;

X is:

phenyl, imidazolyl, pyridinyl, pyrimidinyl, piperdinyl, piperazinyl, pyridazinyl or  
pyrazinyl;

Y is:

a bond or

-CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-, -C(O)-, -O-, -S-, -NH-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -N(CH<sub>3</sub>)-, or -NH-;

each R<sub>1</sub> is independently:

C<sub>3-5</sub> alkyl optionally partially or fully halogenated, and optionally substituted with  
phenyl;

cyclopropyl, cyclopentanyl, cyclohexanyl and bicyclopentanyl optionally substituted with  
one to three methyl groups optionally partially or fully halogenated, CN, hydroxymethyl  
or phenyl; or 2-tetrahydrofuranyl substituted by methyl; or  
trimethyl silyl;

each R<sub>3</sub> is independently:

phenyl, morpholinyl, pyridinyl, pyrimidinyl, pyrrolylidinyl, 2,5-pyrrolidin-dionyl, imidazolyl or pyrazolyl, wherein any of the aforementioned is optionally substituted with C<sub>1-2</sub> alkyl which is optionally partially or fully halogenated;

- 5 C<sub>1-3</sub> alkyl or C<sub>1-3</sub> alkoxy each being optionally partially or fully halogenated or optionally substituted with diethylamino;

OR<sub>18</sub> or C<sub>1-3</sub> alkyl optionally substituted with OR<sub>18</sub>;

- 10 amino or mono- or di-(C<sub>1-3</sub> alkyl)amino optionally substituted with R<sub>19</sub>;

CH<sub>3</sub>C(O)NH-, R<sub>22</sub>O- ; R<sub>23</sub>R<sub>24</sub>NC(O)-; R<sub>26</sub>CH<sub>2</sub>C(O)N(R<sub>21</sub>)- or R<sub>26</sub>C(O)CH<sub>2</sub>N(R<sub>21</sub>)-;

C<sub>2-4</sub>alkenyl substituted by R<sub>23</sub>R<sub>24</sub>NC(O)-; or

15

C<sub>2-4</sub> alkynyl substituted with pyrrolidinyl or pyrrolyl;

R<sub>23</sub> and R<sub>24</sub> are H or R<sub>23</sub> and R<sub>24</sub> taken together optionally form morpholino; and R<sub>26</sub> is morpholino.

20

A further preferred subgeneric aspect of the invention comprises a method of using the compounds of the formula (II), as described in the immediate previous paragraph, and wherein:

25

G is

phenyl, pyridinyl or naphthyl wherein G is substituted by one or more R<sub>1</sub>, R<sub>2</sub> or R<sub>3</sub>;

30

X is:

imidazolyl or pyridinyl;

Y is:

-CH<sub>2</sub>-, -NH-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- or -NH-;

5        Z is morpholino;

each R<sub>1</sub> is independently:

tert-butyl, sec-butyl, tert-amyl or phenyl;

10       R<sub>2</sub> is chloro;

R<sub>3</sub> is independently:

15       methyl, methoxy, methoxymethyl, hydroxypropyl, acetamide, morpholino or  
morpholinocarbonyl.

A still yet further preferred subgeneric aspect of the invention comprises a method of  
using the compounds of the formula (II), as described in the immediate previous  
paragraph, and wherein X is pyridinyl.

20

A still yet further preferred subgeneric aspect of the invention comprises a method of  
using the compounds of the formula (II), as described immediately above, and wherein  
the pyridinyl is attached to Ar via the 3-pyridinyl position.

25

The following compounds are representative of the compounds of formula(II) which are  
useful in the novel methods described herein:

30

1-(3-Cyano-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(3-Fluoro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

35

1-(4-Chloro-2-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

5 1-(2-Chloro-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(3,4-Dimethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

10 1-(3-Iodo-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-m-tolyl-urea;

15 1-(4-Methylsulfanyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(3-Chloro-4-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

20 1-(4-Chloro-3-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2,5-Dichloro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

25 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-naphthalen-2-yl-urea;

1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-phenyl-urea;

30 1-(3-Chloro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(4-Chloro-3-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

35 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(2,4,6-trichloro-phenyl)-urea;

1-(2-Methyl-3-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

40 1-(4-Methyl-2-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

45 1-(2,3-Dichloro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2-Methoxy-5-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2-Chloro-6-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2,4-Dichloro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(4-Methyl-3-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2,4-Dimethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2,3-Dimethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(4-Cyano-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(3,4,5-trimethoxy-phenyl)-urea;

1-Biphenyl-4-yl-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2,5-Difluoro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(3-Chloro-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2-Fluoro-3-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(4-Benzoyloxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2-Methylsulfonyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2-Fluoro-6-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(4-Fluoro-3-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(2,4,5-trimethyl-phenyl)-urea;

5 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(4-trifluoromethyl-phenyl)-urea;

1-(3-Methylsulfanyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

10 1-(2-Methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2-Fluoro-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

15 1-(4-Methoxy-2-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

20 1-(2-Fluoro-5-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(4-Ethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

25 1-(2,5-Dimethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(4,5-Dimethyl-2-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

30 1-(5-Chloro-2-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2-Isopropyl-6-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

35 1-(2-Difluoromethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

40 1-(4-Isopropyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(4-Methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

45 1-(3-Ethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;



1-(2-Ethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(4-Butoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

5 4-{3-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-benzoic acid ethyl ester;

1-(4-Butyl-2-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

10

1-(2,6-Dibromo-4-isopropyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(3-Methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

15

1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(4-trifluoromethylsulfanyl-phenyl)-urea;

20

5-{3-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-isophthalic acid dimethyl ester;

1-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

25

3-{3-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-benzoic acid ethyl ester;

1-(5-tert-Butyl-2-hydroxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

30

1-(2-Hydroxymethyl-4-phenyl-cyclohexyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2-Methylsulfanyl-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

35

1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(4-pentyloxy-biphenyl-3-yl)-urea;

40

4-Methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-benzoic acid methyl ester;

1-(2,5-Diethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

45

1-Benzothiazol-6-yl-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

N-(2,5-Diethoxy-4-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-benzamide;

5

1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(3-phenoxy-phenyl)-urea;

10

1-(5-Ethanesulfonyl-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

4-Methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-N-phenyl-benzamide;

15

1-(2-Methyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2,3-Dimethyl-1H-indol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

20

N-Butyl-4-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-benzenesulfonamide;

25

1-[3-(2-Methyl-[1,3]dioxolan-2-yl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(3-Methoxy-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

30

1-(2,4-Dimethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2-Methyl-4-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

35

1-(2-Methoxy-4-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

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1-(4-Chloro-2-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-Chloro-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

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1-(3,5-Dimethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

- 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(4-trifluoromethoxy-phenyl)-urea;
- 5 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(3-trifluoromethylsulfanyl-phenyl)-urea;
- 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(2-phenoxy-phenyl)-urea;
- 10 1-(2-Methoxy-5-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 15 1-(5-Chloro-2,4-dimethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-(3,5-Bis-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 20 1-(2-tert-Butyl-5-methyl-pyridin-4-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-(3-Methyl-naphthalen-2-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 25 1-(3-tert-Butyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-(4-Methyl-biphenyl-3-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 30 1-(4-tert-Butyl-biphenyl-2-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 35 1-(5-Chloro-2,4-dimethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-(5-Isopropyl-2-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 40 1-(5-sec-Butyl-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 45 1-(5-tert-Butyl-2-methoxy-3-propyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxymethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

5 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methyl-phenyl)-3-(4-{6-[(3-methoxy-propyl)-methyl-amino]-pyridin-3-yl}-naphthalen-1-yl)-urea;

10 1-(5-tert-Butyl-2-methyl-phenyl)-3-[4-(4-morpholin-4-ylmethyl-imidazol-1-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

15 1-(5-tert-Butyl-2-methyl-phenyl)-3-{4-[6-(3-methoxy-propylamino)-pyridin-3-yl]-naphthalen-1-yl}-urea;

20 1-(5-tert-Butyl-2-methyl-pyridin-3-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-morpholin-4-yl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

25 1-(6-tert-Butyl-2-chloro-3-methyl-pyridin-4-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(3-trifluoromethyl-phenyl)-urea;

30 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(4-trifluoromethoxy-phenyl)-urea;

35 1-[5-(1,1-Dimethyl-propyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-2-(1H-pyrazol-4-yl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

40 1-[5-tert-Butyl-2-(2-methyl-pyrimidin-5-yl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-2-(3-hydroxy-propyl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

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1-[5-tert-Butyl-2-(3-morpholin-4-yl-3-oxo-propyl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

5 1-[5-tert-Butyl-2-(morpholine-4-carbonyl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-acetamide;

10 2-(5-tert-Butyl-2-methoxy-phenyl)-N-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-acetamide;

1-(3-Amino-5-tert-butyl-2-methoxy-phenyl)-3-[4-(6-methyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

15 1-(5-tert-Butyl-2-ethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

20 N-(5-tert-Butyl-2-methoxy-4-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-methanesulfonamide;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(4-morpholin-4-ylmethyl-piperidin-1-yl)-naphthalen-1-yl]-urea;

25 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(2-morpholin-4-ylmethyl-pyrimidin-5-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-pyridin-3-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

30 2,2,2-Trifluoro-ethanesulfonic acid (5-tert-butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-amide

and the pharmaceutically acceptable derivatives thereof.

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In addition to the abovementioned representative compounds the following prophetic compounds of the formula(II) may be useful in the novel methods described herein:

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1-[4-(6-{[Bis-(2-cyano-ethyl)-amino]-methyl}-pyridin-3-yl)-naphthalen-1-yl]-3-(5-tert-butyl-2-methoxy-phenyl)-urea

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1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[4-(2-methyl-3-oxo-piperazin-1-ylmethyl)-phenyl]-naphthalen-1-yl}-urea

1-[4-(6-{{Bis-(2-methoxy-ethyl)-amino}-methyl}-pyridin-3-yl)-naphthalen-1-yl]-3-(5-tert-butyl-2-methoxy-phenyl)-urea

5 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2-methyl-3-oxo-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(1-oxo-1,4-thiomorpholin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

10 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-thiomorpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

15 1-(5-tert-Butyl-2-methyl-phenyl)-3-{4-[6-(1-oxo-1,4-thiomorpholin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methyl-phenyl)-3-{4-[6-(2-methyl-3-oxo-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

20 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[4-(1-oxo-1,4-thiomorpholin-4-ylmethyl)-phenyl]-naphthalen-1-yl}-urea;

1-[4-(4-{{Bis-(2-cyano-ethyl)-amino}-methyl}-phenyl)-naphthalen-1-yl]-3-(5-tert-butyl-2-methoxy-phenyl)-urea;

25 1-(2-Methoxy-5-pentafluoroethyl-phenyl)-3-[4-(4-morpholin-4-ylmethyl-piperidin-1-yl)-naphthalen-1-yl]-urea;

1-(2-Methoxy-5-trifluoromethyl-pyridin-3-yl)-3-{4-[2-(4-oxo-piperidin-1-ylmethyl)-pyrimidin-5-yl]-naphthalen-1-yl}-urea;

30 1-(2-Methoxy-5-trimethylsilyl-phenyl)-3-{4-[4-(tetrahydro-pyran-4-ylamino)-phenyl]-naphthalen-1-yl}-urea;

35 1-(3-Methoxy-naphthalen-2-yl)-3-[4-(4-morpholin-4-ylmethyl-piperidin-1-yl)-naphthalen-1-yl]-urea;

1-(3-Methyl-naphthalen-2-yl)-3-[4-(4-morpholin-4-ylmethyl-phenyl)-naphthalen-1-yl]-urea;

40 1-(3-tert-Butyl-5-methanesulfinyl-phenyl)-3-{4-[6-(1-methyl-piperidin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(3-tert-Butyl-phenyl)-3-[4-(3-pyridin-3-yl-propoxy)-naphthalen-1-yl]-urea;

45 1-(3-tert-Butyl-phenyl)-3-[4-(4-morpholin-4-ylmethyl-phenyl)-naphthalen-1-yl]-urea;

1-(4-Methoxy-biphenyl-3-yl)-3-{4-[4-(tetrahydro-pyran-4-ylmethyl)-imidazol-1-yl]-naphthalen-1-yl}-urea;

5 1-(4-Methyl-biphenyl-3-yl)-3-{4-[4-(2-pyridin-4-yl-ethyl)-piperazin-1-yl]-naphthalen-1-yl}-urea;

1-(4-tert-Butyl-biphenyl-2-yl)-3-[4-(pyridin-4-ylmethoxy)-naphthalen-1-yl]-urea;

10 1-(4-tert-Butyl-biphenyl-2-yl)-3-{4-[2-(1-oxo-1,4-thiomorpholin-4-ylmethyl)-3H-imidazol-4-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-hydroxy-phenyl)-3-[4-(5-morpholin-4-ylmethyl-pyrazin-2-yl)-naphthalen-1-yl]-urea;

15 1-(5-tert-Butyl-2-methoxy-3-propyl-phenyl)-3-{4-[4-(pyrrolidine-1-carbonyl)-phenyl]-naphthalen-1-yl}-urea;

20 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(2-morpholin-4-ylmethyl-pyrimidin-5-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(4-thiomorpholin-4-ylmethyl-phenyl)-naphthalen-1-yl]-urea;

25 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-phenyl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[4-(tetrahydro-pyran-4-ylamino)-phenyl]-naphthalen-1-yl}-urea;

30 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

35 1-(5-tert-Butyl-2-methoxy-pyridin-3-yl)-3-{4-[6-(4-oxo-piperidin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methyl-benzooxazol-7-yl)-3-[4-(6-pyridin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

40 1-(5-tert-Butyl-2-methyl-phenyl)-3-[4-(4-morpholin-4-ylmethyl-phenyl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-phenoxy-phenyl)-3-{4-[6-(tetrahydro-pyran-4-yloxy)-pyridin-3-yl]-naphthalen-1-yl}-urea;

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1-(5-tert-Butyl-2-pyrrolidin-1-yl-phenyl)-3-[4-(4-methoxy-6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

5 1-(5-tert-Butyl-2-pyrrolidin-1-yl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-3-cyano-2-methoxy-phenyl)-3-{4-[2-(2,6-dimethyl-morpholin-4-ylmethyl)-pyrimidin-5-yl]-naphthalen-1-yl}-urea;

10 1-(5-tert-Butyl-4'-dimethylamino-biphenyl-3-yl)-3-[4-(2-morpholin-4-ylmethyl-pyrimidin-5-yl)-naphthalen-1-yl]-urea;

1-(6-Methoxy-3,3-dimethyl-indan-5-yl)-3-{4-[4-(morpholine-4-carbonyl)-phenyl]-naphthalen-1-yl}-urea;

15 1-(6-tert-Butyl-2-chloro-3-methyl-pyridin-4-yl)-3-[4-(6-thiomorpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

20 1-(6-tert-Butyl-benzo[1,3]dioxol-4-yl)-3-{4-[6-(morpholin-4-ylamino)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(7-Methoxy-1,4,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-3-{4-[6-(tetrahydro-pyran-4-yloxy)-pyridin-3-yl]-naphthalen-1-yl}-urea;

25 1-(7-tert-Butyl-2,4-dimethyl-benzooxazol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[2-Methoxy-5-(1-methyl-1-phenyl-ethyl)-phenyl]-3-{4-[6-(2-pyridin-4-yl-ethyl)-pyridazin-3-yl]-naphthalen-1-yl}-urea;

30 1-[2-Methoxy-5-(1-methyl-cyclohexyl)-phenyl]-3-{4-[4-(1-methyl-piperidin-4-ylsulfanyl)-phenyl]-naphthalen-1-yl}-urea;

35 1-[2-Methoxy-5-(1-methyl-cyclopropyl)-phenyl]-3-[4-(2-morpholin-4-ylmethyl-pyrimidin-5-yl)-naphthalen-1-yl]-urea;

1-[2-Methoxy-5-(2-methyl-tetrahydro-furan-2-yl)-phenyl]-3-[4-(5-morpholin-4-ylmethyl-pyridin-2-yl)-naphthalen-1-yl]-urea;

40 1-[2-Methoxy-5-(3-trifluoromethyl-bicyclo[1.1.1]pent-1-yl)-phenyl]-3-[4-(4-morpholin-4-ylmethyl-phenyl)-naphthalen-1-yl]-urea;

1-[3-tert-Butyl-5-(1-methyl-1H-imidazol-4-yl)-phenyl]-3-[4-(5-morpholin-4-ylmethyl-pyridin-2-yl)-naphthalen-1-yl]-urea;

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1-[3-tert-Butyl-5-(2-pyrrolidin-1-yl-ethyl)-phenyl]-3-{4-[6-(1-methyl-piperidin-4-yloxy)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-[3-tert-Butyl-5-(3-pyrrolidin-1-yl-prop-1-ynyl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[4-(6-Imidazol-1-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-[2-methoxy-5-(1-phenyl-cyclopropyl)-phenyl]-urea;

1-[5-(1,1-Dimethyl-propyl)-2-methoxy-phenyl]-3-[4-(4-thiomorpholin-4-ylmethyl-phenyl)-naphthalen-1-yl]-urea;

1-[5-(1-Cyano-cyclopropyl)-2-methoxy-phenyl]-3-[4-(2-morpholin-4-ylmethyl-pyrimidin-5-yl)-naphthalen-1-yl]-urea;

1-[5-(1-Hydroxymethyl-cyclopropyl)-2-methoxy-phenyl]-3-[4-(4-morpholin-4-ylmethyl-phenyl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-1-(2-diethylamino-ethyl)-2-oxo-1,2-dihydro-pyridin-3-yl]-3-{4-[6-(1-methyl-piperidin-4-yloxy)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-[5-tert-Butyl-2-(1H-pyrazol-4-yl)-phenyl]-3-[4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-2-(1H-pyrazol-4-yl)-phenyl]-3-{4-[4-(4-methyl-piperazine-1-carbonyl)-phenyl]-naphthalen-1-yl}-urea;

1-[5-tert-Butyl-2-(2,5-dioxo-pyrrolidin-1-yl)-phenyl]-3-{4-[6-(1H-imidazol-2-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-[5-tert-Butyl-2-(2-methyl-pyrimidin-5-yl)-phenyl]-3-[4-(5-pyridin-4-ylmethyl-pyridin-2-yl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-2-(2-morpholin-4-yl-2-oxo-ethoxy)-phenyl]-3-{4-[6-(2-pyridin-4-yl-ethyl)-pyridazin-3-yl]-naphthalen-1-yl}-urea;

1-[5-tert-Butyl-2-(2-morpholin-4-yl-2-oxo-ethylamino)-phenyl]-3-{4-[4-(1-methyl-piperidin-4-ylamino)-piperidin-1-yl]-naphthalen-1-yl}-urea;

1-[5-tert-Butyl-2-(6-methyl-pyridin-3-yl)-phenyl]-3-{4-[5-(2-pyrrolidin-1-yl-ethyl)-pyridin-2-yl]-naphthalen-1-yl}-urea;

1-[5-tert-Butyl-2-methoxy-3-(3-morpholin-4-yl-3-oxo-propenyl)-phenyl]-3-[4-(6-pyrrolidin-1-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-3-(2-diethylamino-ethoxy)-2-methoxy-phenyl]-3-{4-[4-(tetrahydro-pyran-4-yloxy)-phenyl]-naphthalen-1-yl}-urea;

1-[5-tert-Butyl-3-(2-pyrrolidin-1-yl-ethyl)-benzofuran-7-yl]-3-[4-(4-morpholin-4-ylmethyl-phenyl)-naphthalen-1-yl]-urea;

1-[6-tert-Butyl-4-(2-dimethylamino-ethyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl]-3-{4-[6-(thiomorpholin-4-ylamino)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-{5-tert-Butyl-2-methoxy-3-[2-(1-methyl-piperidin-4-yloxy)-ethyl]-phenyl}-3-[4-(4-morpholin-4-ylmethyl-phenyl)-naphthalen-1-yl]-urea;

2-(4-tert-Butyl-2-{3-[4-(5-pyrrolidin-1-ylmethyl-pyridin-2-yl)-naphthalen-1-yl]-ureido}-phenoxy)-N-methyl-acetamide;

2-[4-tert-Butyl-2-(3-{4-[6-(2,6-dimethyl-morpholin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-ureido)-phenoxy]-acetamide;

3-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-pyrrolidin-1-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-acrylamide;

3-{3-tert-Butyl-5-[3-(4-{4-[2-(1-oxo-1,4-thiazolidin-3-yl)-ethyl]-phenyl}-naphthalen-1-yl)-ureido]-phenyl}-N,N-dimethyl-propionamide;

3-{4-[3-(5-tert-Butyl-2-methoxy-phenyl)-ureido]-naphthalen-1-yl}-benzamide;

4-tert-Butyl-2-{3-[4-(2-chloro-4-morpholin-4-ylmethyl-phenyl)-naphthalen-1-yl]-ureido}-benzamide;

N-(4-tert-Butyl-2-{3-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-2-morpholin-4-yl-acetamide;

N-[3-tert-Butyl-5-(3-{4-[5-(tetrahydro-pyran-4-ylamino)-pyridin-2-yl]-naphthalen-1-yl}-ureido)-phenyl]-2-morpholin-4-yl-acetamide;

N-[4-tert-Butyl-2-(3-{4-[4-(1-methyl-piperidin-4-yloxy)-phenyl]-naphthalen-1-yl}-ureido)-phenyl]-acetamide

and the pharmaceutically acceptable derivatives thereof.

In another embodiment of the invention there are provided the following compounds of formula(II) which are useful in the novel methods described herein:

1-(2-tert-Butyl-5-methyl-pyridin-4-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

5 1-(3-Methyl-naphthalen-2-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(3-tert-Butyl-phenyl)-3-[4-(4-morpholin-4-ylmethyl-phenyl)-naphthalen-1-yl]-urea;

10 1-(3-tert-Butyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(4-Methyl-biphenyl-3-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

15 1-(4-tert-Butyl-biphenyl-2-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

20 1-(5-Chloro-2,4-dimethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-Isopropyl-2-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

25 1-(5-sec-Butyl-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-3-propyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

30 1-(5-tert-Butyl-2-methoxymethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

35 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(2-morpholin-4-ylmethyl-pyrimidin-5-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(4-thiomorpholin-4-ylmethyl-phenyl)-naphthalen-1-yl]-urea;

40 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-phenyl)-naphthalen-1-yl]-urea;

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1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[4-(tetrahydro-pyran-4-ylamino)-phenyl]-naphthalen-1-yl}-urea;

5 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methyl-phenyl)-3-(4-{6-[(3-methoxy-propyl)-methyl-amino]-pyridin-3-yl}-naphthalen-1-yl)-urea;

10 1-(5-tert-Butyl-2-methyl-phenyl)-3-[4-(4-morpholin-4-ylmethyl-imidazol-1-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methyl-phenyl)-3-[4-(4-morpholin-4-ylmethyl-phenyl)-naphthalen-1-yl]-urea;

15 1-(5-tert-Butyl-2-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

20 1-(5-tert-Butyl-2-methyl-phenyl)-3-{4-[6-(3-methoxy-propylamino)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methyl-pyridin-3-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

25 1-(5-tert-Butyl-2-morpholin-4-yl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(6-tert-Butyl-2-chloro-3-methyl-pyridin-4-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

30 1-(6-tert-Butyl-2-chloro-3-methyl-pyridin-4-yl)-3-[4-(6-thiomorpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

35 1-[2-Methoxy-5-(1-methyl-cyclopropyl)-phenyl]-3-[4-(2-morpholin-4-ylmethyl-pyrimidin-5-yl)-naphthalen-1-yl]-urea;

1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(3-trifluoromethyl-phenyl)-urea;

40 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(4-trifluoromethoxy-phenyl)-urea;

1-[5-(1,1-Dimethyl-propyl)-2-methoxy-phenyl]-3-[4-(4-thiomorpholin-4-ylmethyl-phenyl)-naphthalen-1-yl]-urea;

45

1-[5-(1,1-Dimethyl-propyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

5 1-[5-(1-Cyano-cyclopropyl)-2-methoxy-phenyl]-3-[4-(2-morpholin-4-ylmethyl-pyrimidin-5-yl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-2-(1H-pyrazol-4-yl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

10 1-[5-tert-Butyl-2-(2-methyl-pyrimidin-5-yl)-phenyl]-3-[4-(5-pyridin-4-ylmethyl-pyridin-2-yl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-2-(2-methyl-pyrimidin-5-yl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

15 1-[5-tert-Butyl-2-(3-hydroxy-propyl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

20 1-[5-tert-Butyl-2-(3-morpholin-4-yl-3-oxo-propyl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-2-(morpholine-4-carbonyl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

25 2-[4-tert-Butyl-2-(3-{4-[6-(2,6-dimethyl-morpholin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-ureido)-phenoxy]-acetamide;

3-[4-[3-(5-tert-Butyl-2-methoxy-phenyl)-ureido]-naphthalen-1-yl]-benzamide;

30 4-tert-Butyl-2-{3-[4-(2-chloro-4-morpholin-4-ylmethyl-phenyl)-naphthalen-1-yl]-ureido}-benzamide;

and the pharmaceutically acceptable derivatives thereof.

35

In another embodiment of the invention there are provided the following compounds of formula(II) which are useful in the novel methods described herein:

40

1-(2-tert-Butyl-5-methyl-pyridin-4-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

45

1-(3-tert-Butyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(4-Methyl-biphenyl-3-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

5 1-(4-tert-Butyl-biphenyl-2-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-Isopropyl-2-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

10 1-(5-sec-Butyl-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

15 1-(5-tert-Butyl-2-methoxymethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

20 1-(5-tert-Butyl-2-methyl-phenyl)-3-(4-{6-[(3-methoxy-propyl)-methyl-amino]-pyridin-3-yl}-naphthalen-1-yl)-urea;

1-(5-tert-Butyl-2-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

25 1-(5-tert-Butyl-2-methyl-pyridin-3-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

30 1-[5-(1,1-Dimethyl-propyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-2-(1H-pyrazol-4-yl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

35 1-[5-tert-Butyl-2-(2-methyl-pyrimidin-5-yl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

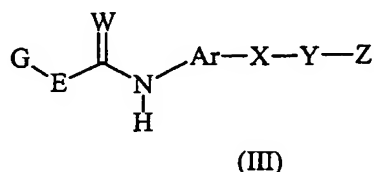
1-[5-tert-Butyl-2-(3-hydroxy-propyl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

40 1-[5-tert-Butyl-2-(morpholine-4-carbonyl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

45 N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-acetamide

and the pharmaceutically acceptable derivatives thereof.

In a fourth broad generic aspect, there is provided a method of treating a cytokine mediated disease or condition chosen from: acute and chronic inflammation in the lung caused by inhalation of smoke, endometriosis, Behcet's disease, uveitis, ankylosing spondylitis, pancreatitis, cancer, Lyme disease, restenosis following percutaneous transluminal coronary angioplasty, Alzheimer's disease, traumatic arthritis, sepsis, chronic obstructive pulmonary disease and congestive heart failure, said method comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of the formula (III) disclosed in WO 00/55139 which is the PCT case of US application serial no. 09/505,582:



wherein:

E is carbon or a heteroatom group chosen from -O-, -NH- and -S-;

G is :  
an aromatic C<sub>6-10</sub> carbocycle or a nonaromatic C<sub>3-10</sub>carbocycle saturated or unsaturated;  
a 6-14 membered monocyclic, bicyclic or tricyclic heteroaryl containing 1 or more heteroatoms chosen from O, N and S;

a 6-8 membered monocyclic heterocycle containing one or more heteroatoms chosen from O, N and S;

or

an 8-11 membered bicyclic heterocycle, containing one or more heteroatoms chosen from

5 O, N and S;

wherein G is optionally substituted by one or more R<sub>1</sub>, R<sub>2</sub> or R<sub>3</sub>;

Ar is:

10 phenyl, naphthyl, quinoliny, isoquinoliny, tetrahydronaphthyl, tetrahydroquinoliny, tetrahydroisoquinoliny, benzimidazolyl, benzofuranyl, dihydrobenzofuranyl, indoliny, benzothienyl, dihydrobenzothienyl, indanyl, indenyl or indolyl each being optionally substituted by one or more R<sub>4</sub> or R<sub>5</sub>;

15 X is:

a C<sub>5-8</sub> cycloalkyl or cycloalkenyl optionally substituted with one to two oxo groups or one to three C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy or C<sub>1-4</sub> alkylamino chains each being branched or unbranched;

20 aryl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyridinonyl, dihydropyridinonyl, maleimidyl, dihydromaleimidyl, piperdinyl, benzimidazole, 3H-imidazo[4,5-b]pyridine, piperazinyl, pyridazinyl or pyrazinyl; each being optionally independently substituted with one to three C<sub>1-4</sub> alkyl, C<sub>1-4</sub>alkoxy, hydroxy, nitrile, amino, mono- or di-(C<sub>1-3</sub> alkyl)amino, mono- or di-(C<sub>1-3</sub> alkylamino)carbonyl, NH<sub>2</sub>C(O), C<sub>1-6</sub>  
25 alkyl-S(O)<sub>m</sub> or halogen;

Y is:

a bond or a C<sub>1-4</sub> saturated or unsaturated branched or unbranched carbon chain optionally  
30 partially or fully halogenated, wherein one or more C atoms are optionally replaced by O, N, or S(O)<sub>m</sub> and wherein Y is optionally independently substituted with one to two oxo



groups, nitrile, phenyl or one or more C<sub>1-4</sub> alkyl optionally substituted by one or more halogen atoms;

Z is:

5

aryl, heteroaryl selected from pyridinyl, piperazinyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl and pyranyl, heterocycle selected from tetrahydropyrimidinyl, cyclohexanonyl, cyclohexanolyl, 2-oxa- or 2-thia-5-aza-bicyclo[2.2.1]heptanyl, pentamethylene sulfidyl, pentamethylene sulfoxidyl,

10

pentamethylene sulfonyl, tetramethylene sulfidyl, tetramethylene sulfoxidyl or tetramethylene sulfonyl, tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxolanonyl, 1,3-dioxanonyl, 1,4-dioxanyl, morpholino, thiomorpholino, thiomorpholino sulfoxidyl, thiomorpholino sulfonyl, piperidinyl, piperidinonyl, pyrrolidinyl and dioxolanyl, each of the aforementioned Z are optionally substituted with one to three halogen, C<sub>1-6</sub>

15

alkyl, C<sub>1-6</sub> alkoxy, C<sub>1-3</sub> alkoxy-C<sub>1-3</sub> alkyl, C<sub>1-6</sub> alkoxy carbonyl, aroyl, C<sub>1-3</sub> acyl, oxo, hydroxy, pyridinyl-C<sub>1-3</sub> alkyl, imidazolyl-C<sub>1-3</sub> alkyl, tetrahydrofuranyl-C<sub>1-3</sub> alkyl, nitrile-C<sub>1-3</sub> alkyl, nitrile, carboxy, phenyl wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkoxy, hydroxy or mono- or di-(C<sub>1-3</sub> alkyl)amino, C<sub>1-6</sub> alkyl-S(O)<sub>m</sub>, or phenyl-S(O)<sub>m</sub> wherein the phenyl ring is optionally substituted with one to two

20

halogen, C<sub>1-6</sub> alkoxy, hydroxy, halogen or mono- or di-(C<sub>1-3</sub> alkyl)amino; or Z is optionally substituted with one to three amino or amino-C<sub>1-3</sub> alkyl wherein the N atom is optionally independently mono- or di-substituted by aminoC<sub>1-6</sub>alkyl, C<sub>1-3</sub>alkyl, arylC<sub>0-3</sub>alkyl, C<sub>1-5</sub> alkoxyC<sub>1-3</sub> alkyl, C<sub>1-5</sub> alkoxy, aroyl, C<sub>1-3</sub>acyl, C<sub>1-3</sub>alkyl-S(O)<sub>m</sub>- or arylC<sub>0-3</sub>alkyl-S(O)<sub>m</sub>- each of the aforementioned alkyl and aryl attached to the amino

25

group is optionally substituted with one to two halogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy; or Z is optionally substituted with one to three aryl, heterocycle or heteroaryl as hereinabove described in this paragraph each in turn is optionally substituted by halogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy;

30

or Z is hydroxy, halogen, nitrile, amino wherein the N atom is optionally independently mono- or di-substituted by C<sub>1-3</sub>acyl, C<sub>1-6</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>1-3</sub>alkyl, C<sub>1-6</sub>alkyl branched

or unbranched, C<sub>1-6</sub>alkoxy, C<sub>1-3</sub>acylamino, nitrileC<sub>1-4</sub>alkyl, C<sub>1-6</sub> alkyl-S(O)<sub>m</sub>, and phenyl-S(O)<sub>m</sub>, wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkoxy, hydroxy or mono- or di-(C<sub>1-3</sub> alkyl)amino;

5 each R<sub>1</sub> is independently:

C<sub>1-10</sub> alkyl branched or unbranched optionally partially or fully halogenated, wherein one or more C atoms are optionally independently replaced by O, N or S(O)<sub>m</sub>, and wherein said C<sub>1-10</sub> alkyl is optionally substituted with one to three C<sub>3-10</sub> cycloalkyl, hydroxy, oxo,  
10 phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrrolidinyl, imidazolyl, pyrazolyl, thienyl, furyl, dioxolanyl, isoxazolyl or isothiazolyl; each of the aforementioned being optionally substituted with one to five groups selected from halogen, C<sub>1-6</sub> alkyl which is optionally partially or fully halogenated, C<sub>3-8</sub> cycloalkanyl, C<sub>5-8</sub> cycloalkenyl, hydroxy, nitrile, C<sub>1-3</sub> alkoxy which is optionally partially or fully  
15 halogenated or NH<sub>2</sub>C(O), mono- or di(C<sub>1-3</sub>alkyl)amino, and mono- or di(C<sub>1-3</sub>alkyl)aminocarbonyl;

or R<sub>1</sub> is

cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, or cycloheptyloxy each  
20 being optionally partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl groups optionally partially or fully halogenated, nitrile, hydroxyC<sub>1-3</sub>alkyl or aryl; or an analog of such cycloalkyl group wherein one to three ring methylene groups are independently replaced by O, S(O)<sub>m</sub>, CHOH, >C=O, >C=S or NH;

25 phenyloxy or benzyloxy each being optionally partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl groups optionally partially or fully halogenated, nitrile, hydroxyC<sub>1-3</sub>alkyl or aryl; or an analog of such cycloaryl group wherein one to two ring methyne groups are independently replaced by N;

30 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclopentanyl, bicyclohexanyl or bicycloheptanyl, each being optionally partially or fully halogenated

and optionally substituted with one to three C<sub>1-3</sub> alkyl optionally partially or fully halogenated, nitrile, hydroxyC<sub>1-3</sub>alkyl or aryl; or an analog of such cycloalkyl group wherein one to three ring methylene groups are independently replaced by O, S(O)<sub>m</sub>, CHOH, >C=O, >C=S or NH;

5

C<sub>3-10</sub> branched or unbranched alkenyl each being optionally partially or fully halogenated, and optionally substituted with one to three C<sub>1-5</sub> branched or unbranched alkyl, phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl or isothiazolyl, each of the aforementioned being substituted  
10 with one to five halogen, C<sub>1-6</sub> alkyl which is optionally partially or fully halogenated, cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, hydroxy, nitrile, C<sub>1-3</sub> alkyloxy which is optionally partially or fully halogenated, NH<sub>2</sub>C(O), mono- or di(C<sub>1-3</sub>alkyl)aminocarbonyl; the C<sub>3-10</sub> branched or unbranched alkenyl being optionally  
15 interrupted by one or more heteroatoms chosen from O, N and S(O)<sub>m</sub>;

cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl or bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C<sub>1-3</sub> alkyl groups;

20

oxo, nitrile, halogen;

silyl containing three C<sub>1-4</sub> alkyl groups optionally partially or fully halogenated; or

25 C<sub>3-6</sub> alkynyl branched or unbranched carbon chain optionally partially or fully halogenated, wherein one or more methylene groups are optionally replaced by O, NH or S(O)<sub>m</sub> and wherein said alkynyl group is optionally independently substituted with one to two oxo groups, hydroxy, pyrroldinyl, pyrrolyl, tetrahydropyranyl, one or more C<sub>1-4</sub> alkyl optionally substituted by one or more halogen atoms, nitrile, morpholino, piperidinyl,  
30 piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl, or mono- or di(C<sub>1-3</sub>alkyl)amino optionally substituted by one or more halogen atoms;

each R<sub>2</sub>, R<sub>4</sub>, and R<sub>5</sub> is

a C<sub>1-6</sub> branched or unbranched alkyl optionally partially or fully halogenated, C<sub>1-6</sub>acyl,  
5 aroyl, C<sub>1-4</sub> branched or unbranched alkoxy, each being optionally partially or fully  
halogenated, halogen, methoxycarbonyl, C<sub>1-3</sub> alkyl-S(O)<sub>m</sub> optionally partially or fully  
halogenated, or phenyl-S(O)<sub>m</sub>;

OR<sub>6</sub>, C<sub>1-6</sub> alkoxy, hydroxy, nitrile, nitro, halogen;

10

or amino-S(O)<sub>m</sub>- wherein the N atom is optionally independently mono- or di-substituted  
by C<sub>1-6</sub>alkyl or arylC<sub>0-3</sub>alkyl, or amino wherein the N atom is optionally independently  
mono- or di-substituted by C<sub>1-3</sub>alkyl, arylC<sub>0-3</sub>alkyl, C<sub>1-6</sub>acyl, C<sub>1-6</sub>alkyl-S(O)<sub>m</sub>- or arylC<sub>0-3</sub>  
3alkyl-S(O)<sub>m</sub>-, each of the aforementioned alkyl and aryl in this subparagraph are  
15 optionally partially or fully halogenated and optionally substituted with one to two C<sub>1-6</sub>  
alkyl or C<sub>1-6</sub> alkoxy;

each R<sub>3</sub> is independently:

20

phenyl, naphthyl, morpholino, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl,  
pyrrolidinyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, [1,3,4]oxadiazol, triazolyl,  
tetrazolyl, thienyl, furyl, tetrahydrofuryl, isoxazolyl, isothiazolyl, quinolinyl,  
isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl,  
benzpyrazolyl, benzothiofuranyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl,  
25 quinoxalinyl, quinazolinyl, purinyl or indazolyl, each of the aforementioned is optionally  
substituted with one to three phenyl, naphthyl, heterocycle or heteroaryl as hereinabove  
described in this paragraph, C<sub>1-6</sub> branched or unbranched alkyl which is optionally  
partially or fully halogenated, cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl,  
cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C<sub>1-5</sub> alkyl,  
30 naphthyl C<sub>1-5</sub> alkyl, halogen, hydroxy, oxo, nitrile, C<sub>1-3</sub> alkoxy optionally partially or fully  
halogenated, phenyloxy, naphthyloxy, heteroaryloxy or heterocycloxy wherein the

heterocyclic or heteroaryl moiety is as hereinabove described in this paragraph, nitro, amino, mono- or di-(C<sub>1-3</sub>alkyl)amino, phenylamino, naphthylamino, heteroaryl or heterocyclic amino wherein the heteroaryl heterocyclic moiety is as hereinabove described in this paragraph, NH<sub>2</sub>C(O), a mono- or di-(C<sub>1-3</sub>alkyl) aminocarbonyl, C<sub>1-5</sub> alkyl-C(O)-C<sub>1-4</sub> alkyl, amino-C<sub>1-5</sub> alkyl, mono- or di-(C<sub>1-5</sub>alkyl)amino, mono- or di-(C<sub>1-3</sub>alkyl)amino-C<sub>1-5</sub> alkyl, amino-S(O)<sub>2</sub>, di-(C<sub>1-3</sub>alkyl)amino-S(O)<sub>2</sub>, R<sub>7</sub>-C<sub>1-5</sub> alkyl, R<sub>8</sub>-C<sub>1-5</sub> alkoxy, R<sub>9</sub>-C(O)-C<sub>1-5</sub> alkyl, R<sub>10</sub>-C<sub>1-5</sub> alkyl(R<sub>11</sub>)N, carboxy-mono- or di-(C<sub>1-5</sub>alkyl)-amino;

a fused aryl selected from benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl, or a fused heteroaryl selected from cyclopentenopyridinyl, cyclohexanopyridinyl, cyclopentanopyrimidinyl, cyclohexanopyrimidinyl, cyclopentanopyrazinyl, cyclohexanopyrazinyl, cyclopentanopyridazinyl, cyclohexanopyridazinyl, cyclopentanoquinolinyl, cyclohexanoquinolinyl, cyclopentanoisoquinolinyl, cyclohexanoisoquinolinyl, cyclopentanoindolyl, cyclohexanoindolyl, cyclopentanobenzimidazolyl, cyclohexanobenzimidazolyl, cyclopentanobenzoxazolyl, cyclohexanobenzoxazolyl, cyclopentanoimidazolyl, cyclohexanoimidazolyl, cyclopentanothienyl and cyclohexanothienyl; wherein the fused aryl or fused heteroaryl ring is independently substituted with zero to three phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, isothiazolyl, C<sub>1-6</sub> alkyl which is optionally partially or fully halogenated, halogen, nitrile, C<sub>1-3</sub> alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heteroaryloxy or heterocycloxy wherein the heteroaryl or heterocyclic moiety is as hereinabove described in this paragraph, nitro, amino, mono- or di-(C<sub>1-3</sub>alkyl)amino, phenylamino, naphthylamino, heteroaryl or heterocyclic amino wherein the heteroaryl or heterocyclic moiety is as hereinabove described in this paragraph, NH<sub>2</sub>C(O), mono- or di-(C<sub>1-3</sub>alkyl)aminocarbonyl, C<sub>1-4</sub> alkyl-OC(O), C<sub>1-5</sub> alkyl-C(O)-C<sub>1-4</sub> alkyl, amino-C<sub>1-5</sub> alkyl, mono- or di-(C<sub>1-3</sub>alkyl)amino-C<sub>1-5</sub> alkyl, R<sub>12</sub>-C<sub>1-5</sub> alkyl, R<sub>13</sub>-C<sub>1-5</sub> alkoxy, R<sub>14</sub>-C(O)-C<sub>1-5</sub> alkyl or R<sub>15</sub>-C<sub>1-5</sub> alkyl(R<sub>16</sub>)N;

cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl or bicycloheptanyl, each being optionally be partially or fully halogenated and optionally substituted with one to three  $C_{1-3}$  alkyl groups, or an analog of such cycloalkyl group wherein one to three ring methylene groups are  
5 independently replaced by O, S, CHOH,  $>C=O$ ,  $>C=S$  or NH;

cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl or bicycloheptenyl, each optionally substituted with one to three  $C_{1-3}$  alkyl groups;

10  $C_{1-4}$  alkyl-phenyl- $C(O)-C_{1-4}$  alkyl-,  $C_{1-4}$  alkyl- $C(O)-C_{1-4}$  alkyl- or  $C_{1-4}$  alkyl-phenyl- $S(O)_m-C_{1-4}$  alkyl-;

$C_{1-6}$  alkyl or  $C_{1-6}$  branched or unbranched alkoxy each of which is optionally partially or  
15 fully halogenated or optionally substituted with  $R_{17}$ ;

$OR_{18}$  or  $C_{1-6}$  alkyl optionally substituted with  $OR_{18}$ ;

amino or mono- or di- $(C_{1-5}alkyl)amino$  optionally substituted with  $R_{19}$ ;

20  $R_{20}C(O)N(R_{21})-$ ,  $R_{22}O-$  or  $R_{23}R_{24}NC(O)-$ ;  $R_{26}(CH_2)_mC(O)N(R_{21})-$ ,  $R_{23}R_{24}NC(O)-C_{1-3}alkoxy$  or  $R_{26}C(O)(CH_2)_mN(R_{21})-$ ;

$C_{2-6}alkenyl$  substituted by  $R_{23}R_{24}NC(O)-$ ;

25  $C_{2-6}alkynyl$  branched or unbranched carbon chain, optionally partially or fully halogenated, wherein one or more methylene groups are optionally replaced by O, NH,  $S(O)_m$  and wherein said alkynyl group is optionally independently substituted with one to two oxo groups, pyrroldinyl, pyrrolyl, morpholino, piperidinyl, piperazinyl, imidazolyl,  
30 phenyl, pyridinyl, tetrazolyl one or more  $C_{1-4}$  alkyl optionally substituted by one or more halogen atoms, nitrile, morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl,

pyridinyl, tetrazolyl, or mono- or di-(C<sub>1-4</sub> alkyl)amino optionally substituted by one or more halogen atoms;

C<sub>1-6</sub>acyl or aroyl;

5

R<sub>6</sub> is a:

C<sub>1-4</sub> alkyl optionally partially or fully halogenated and optionally substituted with R<sub>26</sub>;

10 each R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, R<sub>12</sub>, R<sub>13</sub>, R<sub>14</sub>, R<sub>15</sub>, R<sub>17</sub>, R<sub>19</sub>, R<sub>25</sub> and R<sub>26</sub> is independently:  
nitrile, phenyl, morpholino, piperidinyl, piperazinyl, imidazolyl, pyridinyl, tetrazolyl,  
amino or mono- or di-(C<sub>1-4</sub>alkyl)amino optionally partially or fully halogenated;

each R<sub>11</sub> and R<sub>16</sub> is independently:

15 hydrogen or C<sub>1-4</sub> alkyl optionally partially or fully halogenated;

R<sub>18</sub> is independently:

hydrogen or a C<sub>1-4</sub> alkyl optionally independently substituted with oxo or R<sub>25</sub>;

20 R<sub>20</sub> is independently:

C<sub>1-10</sub> alkyl optionally partially or fully halogenated, phenyl, or pyridinyl;

R<sub>21</sub> is independently:

hydrogen or C<sub>1-3</sub> alkyl optionally partially or fully halogenated;

25

each R<sub>22</sub>, R<sub>23</sub> and R<sub>24</sub> is independently:

hydrogen, C<sub>1-6</sub> alkyl optionally partially or fully halogenated, said C<sub>1-6</sub> alkyl is optionally interrupted by one or more O, N or S, said C<sub>1-6</sub> alkyl also being independently optionally substituted by mono- or di-(C<sub>1-3</sub>alkyl)aminocarbonyl, phenyl, pyridinyl, amino or mono-  
30 or di-(C<sub>1-4</sub>alkyl)amino each of which is optionally partially or fully halogenated and optionally substituted with mono- or di-(C<sub>1-3</sub>alkyl)amino;

or R<sub>23</sub> and R<sub>24</sub> taken together optionally form a heterocyclic or heteroaryl ring;

m = 0, 1 or 2;

5 W is O or S and

the pharmaceutically acceptable derivatives thereof.

10 A preferred subgeneric aspect of the invention comprises a method of using the compounds of the formula(III) as provided above and wherein:

E is -CH<sub>2</sub>-, -NH- or -O-;

W is O;

and

15

G is:

phenyl, naphthyl, benzocyclobutanyl, dihydronaphthyl, tetrahydronaphthyl,  
benzocycloheptanyl, benzocycloheptenyl, indanyl, indenyl;

20 pyridinyl, pyridonyl, quinolinyl, dihydroquinolinyl, tetrahydroquinoyl, isoquinolinyl,  
tetrahydroisoquinoyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzimidazolyl, benzthiazolyl,  
benzooxazolyl, benzofuranyl, benzothiophenyl, benzpyrazolyl, dihydrobenzofuranyl,  
dibenzofuranyl, dihydrobenzothiophenyl, benzooxazolonyl, benzo[1,4]oxazin-3-onyl,  
benzodioxolyl, benzo[1,3]dioxol-2-onyl, benzofuran-3-onyl, tetrahydrobenzopyranyl,  
25 indolyl, 2,3-dihydro-1H-indolyl, indolinyl, indolonyl, indolinonyl, phthalimidyl,  
chromoyl;

oxetanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, piperidinyl, piperazinyl,  
morpholino, tetrahydropyranyl, dioxanyl, tetramethylene sulfonyl, tetramethylene  
sulfoxidyl, oxazoliny, 3,4-dihydro-2H-benzo[1,4]oxazinyl, thiazoliny, imidazoliny,

30 tertrahydropyridiny, homopiperidinyl, pyrroliny, tetrahydropyrimidinyl,



decahydroquinoliny, decahydroisoquinoliny, thiomorpholino, thiazolidiny,  
dihydrooxaziny, dihydropyrany, oxocany, heptacany, thioxany or dithiany;  
wherein G is optionally substituted by one or more R<sub>1</sub>, R<sub>2</sub> or R<sub>3</sub>.

5

A more preferred subgeneric aspect of the invention comprises a method of using the  
compounds of the formula(III) as provided above and wherein:

E is -NH-;

10

G is phenyl, pyridiny, pyridony, naphthyl, quinoliny, isoquinoliny, pyraziny,  
benzimidazolyl, benzooxazolyl, benzooxazolonyl, benzofurany, benzothiophenyl,  
benzpyrazolyl, dihydrobenzofurany, dihydrobenzothiophenyl, 3,4-dihydro-2H-  
benzo[1,4]oxaziny, indany, indenyl, indolyl, indoliny, indolonyl, 2,3-dihydro-1H-  
indolyl or indolinonyl, wherein G is optionally substituted by one or more R<sub>1</sub>, R<sub>2</sub> or R<sub>3</sub>;

15

Ar is:

naphthyl, quinoliny, isoquinoliny, tetrahydronaphthyl, tetrahydroquinoliny,  
tetrahydroisoquinoliny, indany, indenyl or indolyl each being optionally substituted by  
one or more R<sub>4</sub> or R<sub>5</sub> groups;

20

X is:

phenyl, furany, thienyl, pyrroly, pyrazolyl, imidazolyl, pyridiny, pyrimidiny,  
pyridinonyl, dihydropyridinonyl, maleimidyl, dihydromaleimidyl, piperdiny, piperaziny,  
pyridaziny or pyraziny; each being optionally independently substituted with one to  
three C<sub>1-4</sub> alkyl, C<sub>1-4</sub>alkoxy, hydroxy, nitrile, amino, mono- or di-(C<sub>1-3</sub> alkyl)amino,  
mono- or di-(C<sub>1-3</sub> alkylamino)carbonyl, NH<sub>2</sub>C(O), C<sub>1-6</sub> alkyl-S(O)<sub>m</sub> or halogen;

25

30

Y is:

a bond or

a C<sub>1-4</sub> saturated or unsaturated carbon chain wherein one or more of the C atoms is optionally replaced by O, N, or S(O)<sub>m</sub> and wherein Y is optionally independently substituted with one to two oxo groups, nitrile, phenyl or one or more C<sub>1-4</sub> alkyl optionally substituted by one or more halogen atoms;

Z is:

10 phenyl, heteroaryl selected from pyridinyl, piperazinyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, furanyl, thienyl and pyranal, heterocycle selected from 2-oxa-5-aza-bicyclo[2.2.1]heptanyl, tetrahydropyrimidinyl, pentamethylene sulfidyl, pentamethylene sulfoxidyl, pentamethylene sulfonyl, tetramethylene sulfidyl, tetramethylene sulfoxidyl tetramethylene sulfonyl, tetrahydropyranal, tetrahydrofuranal,  
15 1,3-dioxolanonyl, 1,3-dioxanonyl, 1,4-dioxanyl, morpholino, thiomorpholino, thiomorpholino sulfoxidyl, piperidinyl, piperidinonyl, dihydrothiazolyl, dihydrothiazolyl sulfoxidyl, pyrrolidinyl and dioxolanyl which are optionally substituted with one to three nitrile, C<sub>1-3</sub> alkyl, C<sub>1-3</sub> alkoxy, amino, mono- or di-(C<sub>1-3</sub> alkyl)amino, CONH<sub>2</sub> or OH; or Z is optionally substituted by phenyl, heterocycle or heteroaryl as hereinabove  
20 described in this paragraph each in turn is optionally substituted by halogen, C<sub>1-3</sub> alkyl or C<sub>1-3</sub> alkoxy;

or Z is nitrile, nitrileC<sub>1-3</sub> alkyl, C<sub>1-6</sub> alkyl-S(O)<sub>m</sub>, halogen, hydroxy, C<sub>1-3</sub> alkyl, C<sub>1-3</sub> acylamino, C<sub>1-4</sub> alkoxy, amino, mono- or di-(C<sub>1-3</sub> alkyl)aminocarbonyl, or amino mono or  
25 di-substituted by aminoC<sub>1-6</sub> alkyl or C<sub>1-3</sub>alkoxyC<sub>1-3</sub>alkyl;

each R<sub>1</sub> is independently:

C<sub>1-6</sub> alkyl branched or unbranched optionally partially or fully halogenated, wherein one  
30 or more C atoms are optionally independently replaced by O, N or S(O)<sub>m</sub>, and wherein said C<sub>1-6</sub> alkyl is optionally substituted with one to three C<sub>3-6</sub>cycloalkyl, oxo, phenyl,

dioxolanyl, pyrrolidinyl, furyl, isoxazolyl or isothiazolyl; each of the aforementioned being optionally substituted with one to three groups selected from halogen, C<sub>1-3</sub> alkyl which is optionally partially or fully halogenated, hydroxy, nitrile and C<sub>1-3</sub>alkoxy which is optionally partially or fully halogenated;

5

cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, bicyclopentanyl or bicyclohexanyl, each being optionally partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl groups optionally partially or fully halogenated, nitrile, hydroxyC<sub>1-3</sub>alkyl or phenyl; or an analog of such cycloalkyl group wherein one to three ring methylene groups are independently replaced by O, S, CHOH, >C=O, >C=S or NH;

10

oxo;

C<sub>3-6</sub> alkynyl branched or unbranched carbon chain optionally partially or fully

15

halogenated, wherein one or more methylene groups are optionally replaced by O, NH or S(O)<sub>m</sub> and wherein said alkynyl group is optionally independently substituted with one to two oxo groups, hydroxy, pyrrolidinyl, pyrrolyl, tetrahydropyranyl, C<sub>1-4</sub> alkyl optionally substituted by one or more halogen atoms, nitrile, morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl, or mono- or di(C<sub>1-3</sub>alkyl)amino optionally

20

substituted by one or more halogen atoms;

or

silyl containing three C<sub>1-4</sub> alkyl groups optionally partially or fully halogenated;

25

R<sub>2</sub> is independently:

a C<sub>1-5</sub> branched or unbranched alkyl optionally partially or fully halogenated, acetyl, aroyl, C<sub>1-4</sub> branched or unbranched alkoxy, each being optionally partially or fully halogenated, halogen, methoxycarbonyl, C<sub>1-2</sub> alkyl-S(O)<sub>m</sub> optionally partially or fully

30

halogenated, or phenyl-S(O)<sub>m</sub>;

C<sub>1-3</sub> alkoxy, hydroxy, nitrile, nitro, halogen;

or amino-S(O)<sub>m</sub>- wherein the N atom is optionally independently mono- or di-substituted by C<sub>1-3</sub>alkyl or arylC<sub>0-3</sub>alkyl, or amino wherein the N atom is optionally independently mono- or di-substituted by C<sub>1-3</sub>alkyl, arylC<sub>0-3</sub>alkyl, C<sub>1-3</sub>acyl, C<sub>1-4</sub>alkyl-S(O)<sub>m</sub>- or arylC<sub>0-3</sub>alkyl-S(O)<sub>m</sub>-, each of the aforementioned alkyl and aryl in this subparagraph are optionally partially or fully halogenated and optionally substituted with one to two C<sub>1-3</sub> alkyl or C<sub>1-3</sub> alkoxy;

10 R<sub>3</sub> is independently:

phenyl, morpholino, pyridinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrrolidinyl, imidazolyl, [1,3,4]oxadiazol, pyrazolyl, each is optionally substituted with one to three phenyl, naphthyl, heterocycle or heteroaryl as hereinabove described in this paragraph, C<sub>1-6</sub> alkyl which is optionally partially or fully halogenated, cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C<sub>1-5</sub> alkyl, naphthyl C<sub>1-5</sub> alkyl, halogen, oxo, hydroxy, nitrile, C<sub>1-3</sub> alkoxy optionally partially or fully halogenated, phenyloxy, naphthyloxy, heteroaryloxy or heterocycloxy wherein the heteroaryl or heterocyclic moiety is as hereinabove described in this paragraph, nitro, amino, mono- or di-(C<sub>1-3</sub>alkyl)amino, phenylamino, naphthylamino, heteroaryl or heterocyclic amino wherein the heteroaryl or heterocyclic moiety is as hereinabove described in this paragraph, NH<sub>2</sub>C(O), a mono- or di-(C<sub>1-3</sub>alkyl)aminocarbonyl, C<sub>1-5</sub> alkyl-C(O)-C<sub>1-4</sub> alkyl, mono- or di-(C<sub>1-3</sub>alkyl)amino, mono- or di-(C<sub>1-3</sub>alkylamino-C<sub>1-5</sub> alkyl, mono- or di-(C<sub>1-3</sub>alkyl)amino-S(O)<sub>2</sub>, R<sub>7</sub>-C<sub>1-5</sub> alkyl, R<sub>8</sub>-C<sub>1-5</sub> alkoxy, R<sub>9</sub>-C(O)-C<sub>1-5</sub> alkyl, R<sub>10</sub>-C<sub>1-5</sub> alkyl(R<sub>11</sub>)N, carboxy-mono- or di-(C<sub>1-5</sub>)-alkyl-amino;

C<sub>1-3</sub> alkyl or C<sub>1-4</sub> alkoxy each being optionally partially or fully halogenated or optionally substituted with R<sub>17</sub>;

OR<sub>18</sub> or C<sub>1-6</sub> alkyl optionally substituted with OR<sub>18</sub>;

amino or mono- or di- ( $C_{1-5}$  alkyl)amino optionally substituted with  $R_{19}$ ;

$R_{20}C(O)N(R_{21})-$ ,  $R_{22}O-$ ;  $R_{23}R_{24}NC(O)-$ ;  $R_{26}CH_2C(O)N(R_{21})-$ ,  $R_{23}R_{24}NC(O)-C_{1-2}$ alkoxy  
5 or  $R_{26}C(O)CH_2N(R_{21})-$ ;

$C_{2-4}$ alkenyl substituted by  $R_{23}R_{24}NC(O)-$ ; or

$C_{2-4}$  alkynyl branched or unbranched carbon chain optionally partially or fully  
10 halogenated wherein one of the methylene groups is optionally replaced by O, and  
optionally independently substituted with one to two oxo groups, pyrrolidinyl, pyrrolyl,  
morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl or one or  
more  $C_{1-4}$  alkyl optionally substituted by one or more halogen atoms;

15  $C_{1-3}$ acyl; and

$R_{23}$  and  $R_{24}$  taken together optionally form imidazolyl, piperidinyl, morpholino,  
piperazinyl or a pyridinyl ring.

20 A yet more preferred subgeneric aspect of the invention comprises a method of using the  
compounds of the formula (III), as described in the immediate previous paragraph,  
wherein:

G is phenyl, pyridinyl, pyridonyl, naphthyl, quinolinyl, isoquinolinyl, pyrazinyl, 3,4-  
25 dihydro-2H-benzo[1,4]oxazinyl, benzothiophenyl, dihydrobenzofuranyl,  
dihydrobenzothiophenyl, benzooxazolyl, indanyl, indolyl, indolinyl, indolonyl or  
indolinonyl, wherein G is optionally substituted by one or more  $R_1$ ,  $R_2$  or  $R_3$ ;

Ar is naphthyl;

30 X is

phenyl, imidazolyl, pyridinyl, pyrimidinyl, piperdinyl, piperazinyl, pyridazinyl or pyrazinyl each being optionally independently substituted with one to three C<sub>1-4</sub> alkyl, C<sub>1-4</sub>alkoxy, hydroxy, nitrile, amino, mono- or di-(C<sub>1-3</sub> alkyl)amino, mono- or di-(C<sub>1-3</sub> alkylamino)carbonyl, NH<sub>2</sub>C(O), C<sub>1-6</sub> alkyl-S(O)<sub>m</sub> or halogen;

5

Y is:

a bond or

a C<sub>1-4</sub> saturated carbon chain wherein one or more of the C atoms is optionally replaced by O, N or S and wherein Y is optionally independently substituted with nitrile or oxo;

10

Z is:

phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, dihydrothiazolyl, dihydrothiazolyl sulfoxide, pyranyl, pyrrolidinyl, phenylpiperazinyl, tetrahydropyranyl, tetrahydrofuranlyl, dioxolanyl, 2-oxa-5-aza-bicyclo[2.2.1]heptanyl, morpholino, thiomorpholino, thiomorpholino sulfoxidyl, piperidinyl, piperidinonyl, piperazinyl or tetrahydropyrimidinonyl each of which are optionally substituted with one to two C<sub>1-2</sub> alkyl or C<sub>1-2</sub> alkoxy; or

15

Z is hydroxy, C<sub>1-3</sub> alkyl, C<sub>1-3</sub> alkoxy, C<sub>1-3</sub> acylamino, C<sub>1-3</sub> alkylsulfonyl, nitrile C<sub>1-3</sub> alkyl or amino mono or di-substituted by C<sub>1-3</sub> alkoxyC<sub>1-3</sub> alkyl;

20

each R<sub>1</sub> is independently:

C<sub>1-5</sub> alkyl branched or unbranched optionally partially or fully halogenated, wherein one or more C atoms are optionally independently replaced by O, N or S(O)<sub>m</sub>, and wherein said C<sub>1-5</sub> alkyl is optionally substituted with oxo, dioxolanyl, pyrrolidinyl, furyl or phenyl each optionally substituted with one to three halogen, C<sub>1-3</sub> alkyl which is optionally partially or fully halogenated, hydroxy, nitrile and C<sub>1-3</sub>alkoxy which is optionally partially or fully halogenated;

25  
30

cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, bicyclopentanyl or bicyclohexanyl, each being optionally partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl groups optionally partially or fully halogenated, nitrile, hydroxyC<sub>1-3</sub>alkyl or phenyl; and an analog of cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl,  
5 bicyclopentanyl or bicyclohexanyl wherein one ring methylene group is replaced by O;

oxo;

C<sub>2-4</sub> alkynyl optionally partially or fully halogenated wherein one or more methylene  
10 groups are optionally replaced by O, and optionally independently substituted with one to two oxo groups, hydroxy, pyrrolidinyl, pyrrolyl, tetrahydropyranyl, C<sub>1-4</sub> alkyl optionally substituted by one or more halogen atoms, nitrile, morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl, or mono- or di(C<sub>1-3</sub>alkyl)amino optionally substituted by one or more halogen atoms;

15  
or

silyl containing three C<sub>1-2</sub> alkyl groups optionally partially or fully halogenated;

20 each R<sub>2</sub> is independently:

a C<sub>1-4</sub> alkyl optionally partially or fully halogenated, C<sub>1-4</sub> alkoxy optionally partially or fully halogenated, bromo, chloro, fluoro, methoxycarbonyl, methyl-S(O)<sub>m</sub>, ethyl-S(O)<sub>m</sub> each optionally partially or fully halogenated or phenyl-S(O)<sub>m</sub>;

25 or R<sub>2</sub> is mono- or di-C<sub>1-3</sub>acylamino, amino-S(O)<sub>m</sub> or S(O)<sub>m</sub>amino wherein the N atom is mono- or di-substituted by C<sub>1-3</sub>alkyl or phenyl, nitrile, nitro or amino;

each R<sub>3</sub> is independently:

30 phenyl, morpholino, pyridinyl, pyrimidinyl, pyrrolidinyl, 2,5-pyrrolidin-dionyl, imidazolyl, [1,3,4]oxadiazol, pyrazolyl, each of the aforementioned is optionally

substituted with one to three C<sub>1-3</sub> alkyl which is optionally partially or fully halogenated, halogen, oxo, hydroxy, nitrile and C<sub>1-3</sub> alkoxy optionally partially or fully halogenated;

C<sub>1-3</sub> alkyl or C<sub>1-3</sub> alkoxy optionally partially or fully halogenated or optionally substituted  
5 with R<sub>17</sub>;

OR<sub>18</sub> or C<sub>1-3</sub> alkyl optionally substituted with OR<sub>18</sub>;  
amino or mono- or di-(C<sub>1-3</sub> alkyl)amino optionally substituted with R<sub>19</sub>;

10 R<sub>20</sub>C(O)N(R<sub>21</sub>)-, R<sub>22</sub>O-; R<sub>23</sub>R<sub>24</sub>NC(O)-; R<sub>26</sub>CH<sub>2</sub>C(O)N(R<sub>21</sub>)-, NH<sub>2</sub>C(O)methoxy or  
R<sub>26</sub>C(O)CH<sub>2</sub>N(R<sub>21</sub>)-;

C<sub>2-4</sub> alkenyl substituted by R<sub>23</sub>R<sub>24</sub>NC(O)-; or

15 C<sub>2-4</sub> alkynyl substituted with pyrrolidinyl or pyrrolyl;

C<sub>1-3</sub>acyl and

R<sub>23</sub> and R<sub>24</sub> taken together optionally form morpholino.

20

A yet further preferred subgeneric aspect of the invention comprises a method of using  
the compounds of the formula (III), as described in the immediate previous paragraph,  
25 and wherein:

G is phenyl, pyridinyl, pyridonyl, 2-naphthyl, quinolinyl, isoquinolinyl,  
dihydrobenzofuranyl, indanyl, 5-indolyl, 3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl,  
benzooxalolyl, 2,3-dihydrobenzooxazol-7-yl, 2-oxo-2,3-dihydro-1H-indol-5-yl, indolinyl,  
indolonyl, or indolinonyl, wherein G is optionally substituted by one or more R<sub>1</sub>, R<sub>2</sub> or

30 R<sub>3</sub>;



Ar is 1-naphthyl;

X is:

5 phenyl, imidazolyl, pyridinyl, pyrimidinyl, piperdinyl, piperazinyl, pyridazinyl or pyrazinyl;

Y is:

a bond or

10 -CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-, -C(O)-, -O-, -S-, -NH-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -N(CH<sub>3</sub>)-,  
CH<sub>2</sub>(CN)CH<sub>2</sub>-NH-CH<sub>2</sub> or -NH-;

Z is

15 morpholino, dioxolanyl, tetrahydrofuranyl, pyridinyl, 2-oxa-5-aza-bicyclo[2.2.1]heptanyl,  
C<sub>1-3</sub>alkoxyphenylpiperazinyl, hydroxy, C<sub>1-3</sub>alkyl,  
N,N-diC<sub>1-3</sub>alkoxyC<sub>1-3</sub>alkylamino, C<sub>1-3</sub>acylamino, C<sub>1-3</sub>alkylsulfonyl or nitrileC<sub>1-3</sub>alkyl;

each R<sub>1</sub> is independently:

20

C<sub>1-5</sub> alkyl optionally partially or fully halogenated wherein one or more C atoms are optionally independently replaced by O or N, and wherein said C<sub>1-5</sub> alkyl is optionally substituted with oxo, dioxolanyl, pyrrolidinyl, furyl or phenyl optionally substituted by C<sub>1-3</sub>alkoxy;

25

cyclopropyl, cyclopentanyl, cyclohexanyl and bicyclopentanyl optionally substituted with one to three methyl groups optionally partially or fully halogenated, nitrile, hydroxymethyl or phenyl; or 2-tetrahydrofuranyl substituted by methyl; or trimethyl silyl;

30

propynyl substituted hydroxy or tetrahydropyran-2-yloxy;

$R_2$  is

is mono- or di- $C_{1-3}$ acylamino, amino- $S(O)_m$  or  $S(O)_m$  amino wherein the N atom is mono- or di-substituted by  $C_{1-3}$ alkyl or phenyl, bromo, chloro, fluoro, nitrile, nitro, amino, methylsulfonyl optionally partially or fully halogenated or phenylsulfonyl;

5

each  $R_3$  is independently:

phenyl, morpholino, pyridinyl, pyrimidinyl, pyrrolidinyl, 2,5-pyrrolidin-dionyl, imidazolyl, [1,3,4]oxadiazol or pyrazolyl, each is optionally substituted with  $C_{1-2}$  alkyl which is optionally partially or fully halogenated;

10

$C_{1-3}$  alkyl or  $C_{1-3}$  alkoxy each being optionally partially or fully halogenated or optionally substituted with diethylamino;

15  $OR_{18}$  or  $C_{1-3}$  alkyl optionally substituted with  $OR_{18}$ ;

amino or mono- or di- $(C_{1-3}$  alkyl)amino optionally substituted with  $R_{19}$ ;

$CH_3C(O)NH-$ ,  $R_{22}O-$ ;  $R_{23}R_{24}NC(O)-$ ;  $R_{26}CH_2C(O)N(R_{21})-$ ,  $NH_2C(O)$ methoxy or  $R_{26}C(O)CH_2N(R_{21})-$ ;

20

$C_{2-4}$ alkenyl substituted by  $R_{23}R_{24}NC(O)-$ ; or

$C_{2-4}$  alkynyl substituted with pyrrolidinyl or pyrrolyl;

25

$C_{1-2}$ acyl; and

$R_{23}$  and  $R_{24}$  are H or  $R_{23}$  and  $R_{24}$  taken together optionally form morpholino; and

30  $R_{26}$  is morpholino.

A further preferred subgeneric aspect of the invention comprises a method of using the compounds of the formula (III), as described in the immediate previous paragraph, and wherein:

5

G is

phenyl, pyridinyl, 5-indolyl, 3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl, benzooxalolyl, 2,3-dihydrobenzooxazol-7-yl, 2-oxo-2,3-dihydro-1H-indol-5-yl or 2-naphthyl wherein G is optionally substituted by one or more R<sub>1</sub>, R<sub>2</sub> or R<sub>3</sub>;

10

X is:

imidazolyl, pyridinyl, pyrimidinyl or pyrazinyl;

Y is:

15 

a bond, CH<sub>2</sub>(CN)CH<sub>2</sub>-NH-CH<sub>2</sub>-, -CH<sub>2</sub>-, -NH-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- or -NH-;

Z is morpholin-4yl, dioxolan-2yl, tetrahydrofuranyl, pyridinyl, 2-oxa-5-azabicyclo[2.2.1]hept-5yl, methoxyphenylpiperazinyl, hydroxy, methyl, N,N-dimethoxyethylamino, acetylamino, methylsulfonyl or cyanoethyl;

20

each R<sub>1</sub> is independently:

tert-butyl, sec-butyl, tert-amyl, phenyl, tetrahydropyran-2-yloxypropynyl, hydroxypropynyl, trihalomethyl, 2,2-diethylpropionyl or cyclohexanyl;

25

R<sub>2</sub> is chloro, nitro, amino, nitrile, methylsulfonylamino, diacetylamino, phenylsulfonylamino, N,N-di(methylsulfonyl)amino, methylsulfonyl or trihalomethylsulfonyl;

R<sub>3</sub> is independently:

30

methyl, C<sub>1-3</sub> alkoxy, methoxymethyl, hydroxypropyl, dimethylamino, C<sub>1-4</sub>alkylamino, NH<sub>2</sub>C(O)methoxy, acetyl, pyrrolidinyl, imidazolyl, pyrazolyl, morpholino or morpholinocarbonyl.

5

A still yet further preferred subgeneric aspect of the invention comprises a method of using the compounds of the formula (III), as described in the immediate previous paragraph, and wherein:

10

X is pyridinyl.

A still yet further preferred subgeneric aspect of the invention comprises a method of using the compounds of the formula (III), as described immediately above, and wherein

15

the pyridinyl is attached to Ar via the 3-pyridinyl position.

The following compounds are representative of the compounds of formula(II) which are useful in the novel methods described herein:

20

1-(4-tert-Butyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

25

1-(5-tert-Butyl-2-methyl-phenyl)-3-[4-(4-morpholin-4-ylmethyl-piperidin-1-yl)-naphthalen-1-yl]-urea;

1-(6-Chloro-4-trifluoromethyl-pyridin-2-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

30

1-(4-Difluoromethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

35

1-(3-Methyl-naphthalen-2-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[2-Methoxy-5-(1-methyl-1-phenyl-ethyl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

(5-tert-Butyl-2-methyl-phenyl)-carbamic acid 3-(5-{4-[3-(5-tert-butyl-2-methyl-phenyl)-ureido]-naphthalen-1-yl}-pyridin-2-ylamino)-propyl ester;

5 1-(6-tert-Butyl-benzo[1,3]dioxol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-acetamide;

10 1,3-Bis-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-3-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-2-hydroxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

15 1-[5-tert-Butyl-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-3-(2,3-dihydroxy-propyl)-2-hydroxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

20 1-(2,3-Dimethyl-1H-indol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

25 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(2-p-tolyloxy-5-trifluoromethyl-phenyl)-urea;

1-[2-(2-Methoxy-phenoxy)-5-trifluoromethyl-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

30 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-naphthalen-1-yl-urea;

1-{5-tert-Butyl-2-methyl-3-[3-(tetrahydro-pyran-2-yloxy)-prop-1-ynyl]-phenyl}-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

35 1-{5-tert-Butyl-2-[3-(tetrahydro-pyran-2-yloxy)-prop-1-ynyl]-phenyl}-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-Hydroxymethyl-2-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

40 1-(2-Methoxy-dibenzofuran-3-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

45 1-(2,5-Di-tert-butyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[3-(4-Bromo-1-methyl-1H-pyrazol-3-yl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

5 1-(3-Hydroxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(1-Acetyl-2,3-dihydro-1H-indol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

10 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(3-oxazol-5-yl-phenyl)-urea;

1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(3-[1,3,4]oxadiazol-2-yl-phenyl)-urea;

15 1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

20 Furan-2-carboxylic acid (4-tert-butyl-2-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-amide;

1-(2-Methoxy-4-phenylamino-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

25 1-(5-Methoxy-2-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(3-Hydroxy-naphthalen-2-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

30 N,N-Diethyl-4-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-benzenesulfonamide;

35 1-(2,2-Difluoro-benzo[1,3]dioxol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-(1,1-Dimethyl-propyl)-2-phenoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

40 1-[5-(2,2-Dimethyl-propionyl)-2-methyl-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

2-Chloro-5-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-benzoic acid isopropyl ester;

45 1-(4-Amino-3,5-dibromo-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-

naphthalen-1-yl]-urea;

1-[5-tert-Butyl-3-(3-hydroxy-prop-1-ynyl)-2-methyl-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

5

1-[5-tert-Butyl-2-(3-hydroxy-prop-1-ynyl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

10

1-[5-tert-Butyl-3-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-3-(2,3-dihydroxy-propyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

15

1-(5-tert-Butoxy-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-(1-Cyano-cyclopropyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

20

1-[5-tert-Butyl-3-(2-diethylamino-ethyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

25

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-[1,3]dioxolan-2-yl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-pyrrolidin-1-yl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

30

1-(5-tert-Butyl-2-dimethylamino-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-propoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

35

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-hydroxymethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

40

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2,6-dimethyl-morpholin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

2-(5-tert-Butyl-2-methoxy-phenyl)-N-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-acetamide;

45

1-(2-Methoxy-5-phenoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-7-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

- 5 1-(5-tert-Butyl-2-cyclopentyloxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(3-pyridin-3-yl-pyrrolidin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

- 10 1-(5-Cyclohexyl-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

- 15 1-(2,4-Dimethoxy-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(6-tert-Butyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

- 20 1-(5-tert-Butyl-2-methoxy-3-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(3-Amino-5-tert-butyl-2-methoxy-phenyl)-3-[4-(6-methyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

- 25 N-Acetyl-N-(5-tert-butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-acetamide;

- 30 1-(6-tert-Butyl-4-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[6-tert-Butyl-4-(2-morpholin-4-yl-ethyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

- 35 1-(5-tert-Butyl-2-ethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-isopropoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

- 40 1-(5-tert-Butyl-2-imidazol-1-yl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

- 45 N-(5-tert-Butyl-2-methoxy-4-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-methanesulfonamide;



1-(5-tert-Butyl-3-ethylamino-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

5 N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-bis(methanesulfon)amide;

1-[5-tert-Butyl-2-(1-methyl-1H-pyrazol-4-yl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

10 1-(2-Methanesulfinyl-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2-Ethanesulfonyl-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

15 1-[4-(6-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-pyridin-3-yl)-naphthalen-1-yl]-3-(5-tert-butyl-2-methoxy-phenyl)-urea;

20 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(3-dimethylamino-pyrrolidin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

N-[1-(5-{4-[3-(5-tert-Butyl-2-methoxy-phenyl)-ureido]-naphthalen-1-yl}-pyridin-2-ylmethyl)-pyrrolidin-3-yl]-acetamide;

25 1-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-propionamide;

30 1-(5-tert-Butyl-2-methyl-benzooxazol-7-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

35 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(3-trifluoromethanesulfonyl-phenyl)-urea;

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-isobutyramide;

40 2-(4-tert-Butyl-2-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenoxy)-acetamide;

1-(5-tert-Butyl-2-oxo-2,3-dihydro-benzooxazol-7-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

45 1-(6-tert-Butyl-3-cyano-2-methoxymethoxy-pyridin-4-yl)-3-[4-(6-morpholin-4-ylmethyl-

pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(6-tert-Butyl-3-cyano-2-hydroxy-pyridin-4-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

5

1-(5-tert-Butyl-3-cyano-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

10

1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(1,3,3-trimethyl-2,3-dihydro-1H-indol-5-yl)-urea;

1-(5-tert-Butyl-benzooxazol-7-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

15

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-benzenesulfonamide;

Ethanesulfonic acid (5-tert-butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-amide;

20

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(4-morpholin-4-ylmethyl-piperidin-1-yl)-naphthalen-1-yl]-urea;

25

1-[5-tert-Butyl-2-(1-methyl-1H-pyrazol-4-yl)-phenyl]-3-[4-(4-morpholin-4-ylmethyl-piperidin-1-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(2-morpholin-4-ylmethyl-pyrimidin-5-yl)-naphthalen-1-yl]-urea;

30

1-(5-tert-Butyl-2-methylsulfanyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-pyridin-3-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

35

2,2,2-Trifluoro-ethanesulfonic acid (5-tert-butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-amide;

40

N-(5-{4-[3-(5-tert-Butyl-2-methyl-phenyl)-ureido]-naphthalen-1-yl}-pyrazin-2-yl)-methanesulfonamide;

1-[4-(6-{[Bis-(2-cyano-ethyl)-amino]-methyl}-pyridin-3-yl)-naphthalen-1-yl]-3-(5-tert-butyl-2-methoxy-phenyl)-urea;

45

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-thiomorpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

5 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2,6-dimethyl-piperidin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(1-oxo-tetrahydro-thiopyran-4-ylamino)-pyridin-3-yl]-naphthalen-1-yl}-urea;

10 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(tetrahydro-pyran-4-ylamino)-pyridin-3-yl]-naphthalen-1-yl}-urea;

15 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-{{(2-cyano-ethyl)-(tetrahydro-furan-2-ylmethyl)-amino}-methyl}-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2-methoxymethyl-morpholin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

20 1-(5-tert-Butyl-2-methoxy-phenyl)-3-(4-{6-[(2-morpholin-4-yl-ethylamino)-methyl]-pyridin-3-yl}-naphthalen-1-yl)-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2-methyl-3-oxo-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

25 1-(5-{4-[3-(5-tert-Butyl-2-methoxy-phenyl)-ureido]-naphthalen-1-yl}-pyridin-2-ylmethyl)-piperidine-3-carboxylic acid amide;

30 1-(5-{4-[3-(5-tert-Butyl-2-methoxy-phenyl)-ureido]-naphthalen-1-yl}-pyridin-2-ylmethyl)-piperidine-4-carboxylic acid amide;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(1-oxo-114-thiomorpholin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

35 1-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(3-oxo-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

40 1-{4-[6-(4-Acetyl-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-3-(5-tert-butyl-2-methoxy-phenyl)-urea;

45 4-(5-{4-[3-(5-tert-Butyl-2-methoxy-phenyl)-ureido]-naphthalen-1-yl}-pyridin-2-ylmethyl)-piperazine-1-carboxylic acid ethyl ester;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-(4-{6-[(2-pyridin-3-yl-ethylamino)-methyl]-pyridin-3-yl}-naphthalen-1-yl)-urea;

5 1-(5-tert-Butyl-2-methoxy-phenyl)-3-(4-{6-[(tetrahydro-furan-3-ylamino)-methyl]-pyridin-3-yl}-naphthalen-1-yl)-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-{[(2-cyano-ethyl)-pyridin-3-ylmethyl-amino]-methyl}-pyridin-3-yl)-naphthalen-1-yl]-urea;

10 1-(5-tert-Butyl-2-methoxy-phenyl)-3-(4-{6-[(2-methylsulfonyl-ethylamino)-methyl]-pyridin-3-yl}-naphthalen-1-yl)-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

15 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2,6-dimethyl-morpholin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

20 1-(5-tert-Butyl-2-methoxy-phenyl)-3-(4-{6-[(2-piperazin-1-yl-ethylamino)-methyl]-pyridin-3-yl}-naphthalen-1-yl)-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(4-pyrimidin-2-yl-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

25 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(4-pyridin-2-yl-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-(4-{6-[4-(3-methoxy-phenyl)-piperazin-1-ylmethyl]-pyridin-3-yl}-naphthalen-1-yl)-urea;

30 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(morpholine-4-carbonyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

35 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2-thia-5-aza-bicyclo[2.2.1]hept-5-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(5-morpholin-4-ylmethyl-pyrazin-2-yl)-naphthalen-1-yl]-urea;

40 1-(6-tert-Butyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(3-Amino-5-tert-butyl-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

45 N-(5-{4-[3-(5-tert-Butyl-2-methoxy-phenyl)-ureido]-naphthalen-1-yl}-pyridin-2-yl)-

acetamide;

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-N-methyl-acetamide;

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-2,2,2-trifluoro-acetamide;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(pyridin-3-yloxy)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(pyridin-3-ylamino)-pyridin-3-yl]-naphthalen-1-yl}-urea;

[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-carbamic acid 3-tert-butyl-phenyl ester;

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-methanesulfonamide and

the pharmaceutically acceptable derivatives thereof.

In another embodiment of the invention there are provided the following compounds of formula(III) which are useful in the novel methods described herein:

1-(3-Methyl-naphthalen-2-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-acetamide;

1-[5-tert-Butyl-3-(2,3-dihydroxy-propyl)-2-hydroxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2,3-Dimethyl-1H-indol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-{5-tert-Butyl-2-methyl-3-[3-(tetrahydro-pyran-2-yloxy)-prop-1-ynyl]-phenyl}-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-(2,2-Dimethyl-propionyl)-2-methyl-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-3-(3-hydroxy-prop-1-ynyl)-2-methyl-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-2-(3-hydroxy-prop-1-ynyl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-3-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-3-(2,3-dihydroxy-propyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butoxy-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-(1-Cyano-cyclopropyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-3-(2-diethylamino-ethyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-[1,3]dioxolan-2-yl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-pyrrolidin-1-yl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-dimethylamino-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-propoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-hydroxymethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2,6-dimethyl-morpholin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-Cyclohexyl-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2,4-Dimethoxy-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-

yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-3-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

5

1-(3-Amino-5-tert-butyl-2-methoxy-phenyl)-3-[4-(6-methyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

10

N-Acetyl-N-(5-tert-butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-acetamide;

1-(6-tert-Butyl-4-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

15

1-(5-tert-Butyl-2-ethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-isopropoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

20

1-(5-tert-Butyl-2-imidazol-1-yl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

25

1-(5-tert-Butyl-3-ethylamino-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-bis(methanesulfon)amide;

30

1-[5-tert-Butyl-2-(1-methyl-1H-pyrazol-4-yl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2-Methanesulfinyl-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

35

1-[4-(6-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-pyridin-3-yl)-naphthalen-1-yl]-3-(5-tert-butyl-2-methoxy-phenyl)-urea;

40

N-[1-(5-{4-[3-(5-tert-Butyl-2-methoxy-phenyl)-ureido]-naphthalen-1-yl}-pyridin-2-ylmethyl)-pyrrolidin-3-yl]-acetamide;

1-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

45

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-propionamide;

1-(5-tert-Butyl-2-methyl-benzooxazol-7-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

5 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(3-trifluoromethanesulfonyl-phenyl)-urea;

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-isobutyramide;

10 2-(4-tert-Butyl-2-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenoxy)-acetamide;

15 1-(5-tert-Butyl-2-oxo-2,3-dihydro-benzooxazol-7-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-3-cyano-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

20 1-(5-tert-Butyl-benzooxazol-7-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-benzenesulfonamide;

25 Ethanesulfonic acid (5-tert-butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-amide;

30 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(2-morpholin-4-ylmethyl-pyrimidin-5-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methylsulfanyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

35 1-(5-tert-Butyl-2-methoxy-pyridin-3-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

2,2,2-Trifluoro-ethanesulfonic acid (5-tert-butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-amide;

40 N-(5-{4-[3-(5-tert-Butyl-2-methyl-phenyl)-ureido]-naphthalen-1-yl}-pyrazin-2-yl)-methanesulfonamide;

45 1-[4-(6-{[Bis-(2-cyano-ethyl)-amino]-methyl}-pyridin-3-yl)-naphthalen-1-yl]-3-(5-tert-butyl-2-methoxy-phenyl)-urea;



1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

5 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-thiomorpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2,6-dimethyl-piperidin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

10 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(1-oxo-tetrahydro-thiopyran-4-ylamino)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(tetrahydro-pyran-4-ylamino)-pyridin-3-yl]-naphthalen-1-yl}-urea;

15 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-[(2-cyano-ethyl)-(tetrahydro-furan-2-ylmethyl)-amino]-methyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

20 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2-methoxymethyl-morpholin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2-methyl-3-oxo-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

25 1-(5-{4-[3-(5-tert-Butyl-2-methoxy-phenyl)-ureido]-naphthalen-1-yl}-pyridin-2-ylmethyl)-piperidine-3-carboxylic acid amide;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(1-oxo-1,4-thiomorpholin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

30 1-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

35 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(3-oxo-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-(4-{6-[(tetrahydro-furan-3-ylamino)-methyl]-pyridin-3-yl}-naphthalen-1-yl)-urea;

40 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-[(2-cyano-ethyl)-pyridin-3-ylmethyl-amino]-methyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

45 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2,6-dimethyl-morpholin-4-ylmethyl)-

pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-(4-{6-[4-(3-methoxy-phenyl)-piperazin-1-ylmethyl]-pyridin-3-yl}-naphthalen-1-yl)-urea;

5

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(morpholine-4-carbonyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

10

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(5-morpholin-4-ylmethyl-pyrazin-2-yl)-naphthalen-1-yl]-urea;

1-(6-tert-Butyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

15

1-(3-Amino-5-tert-butyl-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

N-(5-{4-[3-(5-tert-Butyl-2-methoxy-phenyl)-ureido]-naphthalen-1-yl}-pyridin-2-yl)-acetamide;

20

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-N-methyl-acetamide;

25

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-2,2,2-trifluoro-acetamide;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(pyridin-3-yloxy)-pyridin-3-yl]-naphthalen-1-yl}-urea;

30

[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-carbamic acid 3-tert-butyl-phenyl ester;

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-methanesulfonamide and

35

the pharmaceutically acceptable derivatives thereof.

40

In addition to the abovementioned compounds the following prophetic compounds of the formula(III) may be useful in the novel methods described herein:

1-(5-tert-Butyl-2-methylsulfanyl-pyridin-3-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

45

1-(5-tert-Butyl-2-chloro-pyridin-3-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methylamino-pyridin-3-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

N-(5-tert-Butyl-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-2-oxo-2H-pyridin-1-yl)-methanesulfonamide;

5-tert-Butyl-7-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-benzooxazole-2-carboxylic acid amide;

2-(5-tert-Butyl-7-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-benzooxazol-2-yl)-acetamide;

5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-benzamide and

the pharmaceutically acceptable derivatives thereof.

The invention includes the use of any compounds of described above containing one or more asymmetric carbon atoms may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be in the R or S configuration, or a combination of configurations.

Some of the compounds of formulas (I), (Ia), (II) and (III) can exist in more than one tautomeric form. The invention includes methods using all such tautomers.

All terms as used herein in this specification, unless otherwise stated, shall be understood in their ordinary meaning as known in the art. For example, "C<sub>1-4</sub>alkoxy" is a C<sub>1-4</sub>alkyl with a terminal oxygen, such as methoxy, ethoxy, propoxy, pentoxy and hexoxy. All alkyl, alkenyl and alkynyl groups shall be understood as being branched or unbranched where structurally possible and unless otherwise specified. Other more specific definitions are as follows:

The term "aroyl" as used in the present specification shall be understood to mean "benzoyl" or "naphthoyl".

5 The term "carbocycle" shall be understood to mean an aliphatic hydrocarbon radical containing from three to twelve carbon atoms. Carbocycles include hydrocarbon rings containing from three to ten carbon atoms. These carbocycles may be either aromatic and non-aromatic ring systems. The non-aromatic ring systems may be mono- or polyunsaturated. Preferred carbocycles include but are not limited to cyclopropyl, 10 cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptanyl, cycloheptenyl, phenyl, indanyl, indenyl, benzocyclobutanyl, dihydronaphthyl, tetrahydronaphthyl, naphthyl, decahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl. Certain terms for cycloalkyl such as cyclobutanyl and cyclobutyl shall be used interchangeably.

15 The term "heterocycle" refers to a stable nonaromatic 4-8 membered (but preferably, 5 or 6 membered) monocyclic or nonaromatic 8-11 membered bicyclic heterocycle radical which may be either saturated or unsaturated. Each heterocycle consists of carbon atoms and one or more, preferably from 1 to 4 heteroatoms selected from nitrogen, oxygen and 20 sulfur. The heterocycle may be attached by any atom of the cycle, which results in the creation of a stable structure. Unless otherwise stated, heterocycles include but are not limited to, for example oxetanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, dioxanyl, tetramethylene sulfonyl, tetramethylene sulfoxidyl, oxazoliny, thiazoliny, imidazoliny, 25 tetrahydropyridiny, homopiperidinyl, pyrroliny, tetrahydropyrimidinyl, decahydroquinoliny, decahydroisoquinoliny, thiomorpholinyl, thiazolidiny, dihydrooxazinyl, dihydropyranyl, oxocanyl, heptacanyl, thioxanyl, dithianyl or 2-oxa- or 2-thia-5-aza-bicyclo[2.2.1]heptanyl.

30 The term "heteroaryl" shall be understood to mean an aromatic 5-8 membered monocyclic or 8-11 membered bicyclic ring containing 1-4 heteroatoms such as N,O and

S. Unless otherwise stated, such heteroaryls include: pyridinyl, pyridonyl, quinolinyl, dihydroquinolinyl, tetrahydroquinoyl, isoquinolinyl, tetrahydroisoquinoyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, benzofuranyl, benzothiophenyl, benzpyrazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl,  
5 benzooxazolonyl, benzo[1,4]oxazin-3-onyl, benzodioxolyl, benzo[1,3]dioxol-2-onyl, tetrahydrobenzopyranyl, indolyl, indolinyl, indolonyl, indolinonyl, phthalimidyl.

The invention includes methods of using pharmaceutically acceptable derivatives of  
10 compounds of formula (I), (Ia), (II) and (III). A "pharmaceutically acceptable derivative" refers to any pharmaceutically acceptable salt or ester, or any other compound which, upon administration to a patient, is capable of providing (directly or indirectly) a compound useful for the invention, or a pharmacologically active metabolite or pharmacologically active residue thereof. A pharmacologically active metabolite shall be  
15 understood to mean any compound of the invention capable of being metabolized enzymatically or chemically. This includes, for example, hydroxylated or oxidized derivative compounds of the formulas (I), (Ia), (II) or (III).

Pharmaceutically acceptable salts include those derived from pharmaceutically  
20 acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfuric, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfuric and benzenesulfonic acids. Other acids, such as oxalic acid, while not themselves pharmaceutically  
25 acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (*e.g.*, sodium), alkaline earth metal (*e.g.*, magnesium), ammonium and  $N-(C_1-C_4 \text{ alkyl})_4^+$  salts.

30 In addition, within the scope of the invention is use of prodrugs of compounds of the formula (I), (Ia), (II) and (III). Prodrugs include those compounds that, upon simple

chemical transformation, are modified to produce compounds of the invention. Simple chemical transformations include hydrolysis, oxidation and reduction. Specifically, when a prodrug is administered to a patient, the prodrug may be transformed into a compound disclosed hereinabove, thereby imparting the desired pharmacological effect.

5

### METHODS OF USE

10 In accordance with the invention, there are provided novel methods of using the compounds of the formulas (I), (Ia), (II) and (III). as described in WO 00/55139 and US application serial number 09/505,582. The compounds disclosed therein effectively block inflammatory cytokine production from cells. The inhibition of cytokine production is an attractive means for preventing and treating a variety of cytokine mediated diseases or  
15 conditions associated with excess cytokine production, *e.g.*, diseases and pathological conditions involving inflammation. Thus, the compounds are described in WO 00/55139 as being useful for the treatment of the following conditions and diseases:  
osteoarthritis, multiple sclerosis, Guillain-Barre syndrome, Crohn's disease, ulcerative colitis, psoriasis, graft versus host disease, systemic lupus erythematosus and insulin-  
20 dependent diabetes mellitus, rheumatoid arthritis, Alzheimer's disease, toxic shock syndrome, diabetes, inflammatory bowel diseases, acute and chronic pain as well as symptoms of inflammation and cardiovascular disease, stroke, myocardial infarction, alone or following thrombolytic therapy, thermal injury, adult respiratory distress syndrome (ARDS), multiple organ injury secondary to trauma, acute glomerulonephritis,  
25 dermatoses with acute inflammatory components, acute purulent meningitis or other central nervous system disorders, hemodialysis, leukopheresis, granulocyte transfusion associated syndromes, and necrotizing enterocolitis.

Suprisingly, it has been discovered for the first time that the compounds disclosed in WO 00/55139 are useful in methods for treating: acute and chronic inflammation in the lung  
30 caused by inhalation of smoke, endometriosis, Behcet's disease, uveitis, ankylosing spondylitis, pancreatitis, cancer, Lyme disease, restenosis following percutaneous

transluminal coronary angioplasty, Alzheimer's disease, traumatic arthritis, sepsis, chronic obstructive pulmonary disease and congestive heart failure.

For therapeutic use, the compounds may be administered in any conventional dosage form in any conventional manner. Routes of administration include, but are not limited to, intravenously, intramuscularly, subcutaneously, intrasynovially, by infusion, sublingually, transdermally, orally, topically or by inhalation. The preferred modes of administration are oral and intravenous.

The compounds may be administered alone or in combination with adjuvants that enhance stability of the inhibitors, facilitate administration of pharmaceutical compositions containing them in certain embodiments, provide increased dissolution or dispersion, increase inhibitory activity, provide adjunct therapy, and the like, including other active ingredients. Advantageously, such combination therapies utilize lower dosages of the conventional therapeutics, thus avoiding possible toxicity and adverse side effects incurred when those agents are used as monotherapies. The above described compounds may be physically combined with the conventional therapeutics or other adjuvants into a single pharmaceutical composition. Reference in this regard may be made to Cappola et al.: US patent application no. 09/902,822 and PCT/US 01/21860 each incorporated by reference herein in their entirety. Advantageously, the compounds may then be administered together in a single dosage form. In some embodiments, the pharmaceutical compositions comprising such combinations of compounds contain at least about 5%, but more preferably at least about 20%, of a compound of formulas (I), (Ia), (II) and (III) (w/w) or a combination thereof. The optimum percentage (w/w) of a compound of the invention may vary and is within the purview of those skilled in the art. Alternatively, the compounds may be administered separately (either serially or in parallel). Separate dosing allows for greater flexibility in the dosing regime.

As mentioned above, dosage forms of the compounds described herein include pharmaceutically acceptable carriers and adjuvants known to those of ordinary skill in the art. These carriers and adjuvants include, for example, ion exchangers, alumina,

aluminum stearate, lecithin, serum proteins, buffer substances, water, salts or electrolytes and cellulose-based substances. Preferred dosage forms include, tablet, capsule, caplet, liquid, solution, suspension, emulsion, lozenges, syrup, reconstitutable powder, granule, suppository and transdermal patch. Methods for preparing such dosage forms are known  
5 (see, for example, H.C. Ansel and N.G. Popovich, *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 5th ed., Lea and Febiger (1990)). Dosage levels and requirements are well-recognized in the art and may be selected by those of ordinary skill in the art from available methods and techniques suitable for a particular patient. In some embodiments, dosage levels range from about 1-1000 mg/dose for a 70 kg patient.  
10 Although one dose per day may be sufficient, up to 5 doses per day may be given. For oral doses, up to 2000 mg/day may be required. As the skilled artisan will appreciate, lower or higher doses may be required depending on particular factors. For instance, specific dosage and treatment regimens will depend on factors such as the patient's general health profile, the severity and course of the patient's disorder or disposition  
15 thereto, and the judgment of the treating physician.

#### GENERAL SYNTHETIC METHODS

20

The compounds described hereinabove may be prepared by Method A, B, or C as illustrated in Scheme I, preferably method C, in WO 00/55139. Starting materials used are either commercially available or easily prepared from commercially available materials known by those skilled in the art. Further reference in this regard may be made  
25 to US application nos. 09/505,582, 09/484,638, 09/714,539, 09/611,109, 09/698,442 and US provisional application no. 60/216,283. Each of the aforementioned incorporated herein by reference in their entirety.

30

#### ASSESSMENT OF BIOLOGICAL PROPERTIES



### Inhibition of TNF Production in THP Cells

The inhibition of cytokine production can be observed by measuring inhibition of TNF $\alpha$  in lipopolysaccharide stimulated THP cells (for example, see W. Prichett *et al.*, 1995, *J. Inflammation*, 45, 97). All cells and reagents were diluted in RPMI 1640 with phenol red and L-glutamine, supplemented with additional L-glutamine (total: 4 mM), penicillin and streptomycin (50 units/ml each) and fetal bovine serum (FBS, 3%) (GIBCO, all conc. final). Assay was performed under sterile conditions; only test compound preparation was nonsterile. Initial stock solutions were made in DMSO followed by dilution into RPMI 1640 2-fold higher than the desired final assay concentration. Confluent THP.1 cells ( $2 \times 10^6$  cells/ml, final conc.; American Type Culture Company, Rockville, MD) were added to 96 well polypropylene round bottomed culture plates (Costar 3790; sterile) containing 125  $\mu$ l test compound (2 fold concentrated) or DMSO vehicle (controls, blanks). DMSO concentration did not exceed 0.2% final. Cell mixture was allowed to preincubate for 30 min, 37°C, 5% CO<sub>2</sub> prior to stimulation with lipopolysaccharide (LPS; 1  $\mu$ g/ml final; Siga L-2630, from E.coli serotype 0111.B4; stored as 1 mg/ml stock in endotoxin screened distilled H<sub>2</sub>O at -80°C). Blanks (unstimulated) received H<sub>2</sub>O vehicle; final incubation volume was 250  $\mu$ l. Overnight incubation (18 - 24 hr) proceeded as described above. Assay was terminated by centrifuging plates 5 min, room temperature, 1600 rpm (400 x g); supernatants were transferred to clean 96 well plates and stored - 80°C until analyzed for human TNF $\alpha$  by a commercially available ELISA kit (Biosource #KHC3015, Camarillo, CA). Data was analyzed by non-linear regression (Hill equation) to generate a dose response curve using SAS Software System (SAS institute, Inc., Cary, NC). The calculated IC<sub>50</sub> value is the concentration of the test compound that caused a 50% decrease in the maximal TNF $\alpha$  production.

Preferred compounds including those from the synthetic examples above were evaluated and had IC<sub>50</sub> < 10  $\mu$ M in this assay.

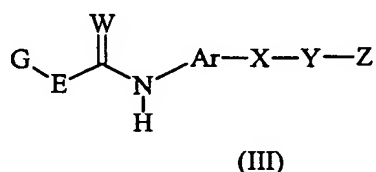
### Inhibition of other cytokines

By similar methods using peripheral blood monocytic cells, appropriate stimuli, and commercially available ELISA kits (or other method of detection such as radioimmunoassay), for a particular cytokine, inhibition of IL-1beta, GM-CSF, IL-6 and IL-8 can be demonstrated for preferred compounds (for example, see J.C. Lee *et al.*, 1988, *Int. J. Immunopharmacol.*, 10, 835).

5

**What is Claimed is:**

1. A method of treating a cytokine mediated disease or condition chosen from acute and chronic inflammation in the lung caused by inhalation of smoke, endometriosis, Behcet's disease, uveitis, ankylosing spondylitis, pancreatitis, cancer, Lyme disease, restenosis following percutaneous transluminal coronary angioplasty, Alzheimer's disease, traumatic arthritis, sepsis, chronic obstructive pulmonary disease and congestive heart failure, said method comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of the formula (III):



wherein:

E is carbon or a heteroatom group chosen from -O-, -NH- and -S-;

G is :

an aromatic C<sub>6-10</sub> carbocycle or a nonaromatic C<sub>3-10</sub>carbocycle saturated or unsaturated;

a 6-14 membered monocyclic, bicyclic or tricyclic heteroaryl containing 1 or more heteroatoms chosen from O, N and S;

a 6-8 membered monocyclic heterocycle containing one or more heteroatoms chosen from O, N and S;

or

an 8-11 membered bicyclic heterocycle, containing one or more heteroatoms chosen from O, N and S;

wherein G is optionally substituted by one or more R<sub>1</sub>, R<sub>2</sub> or R<sub>3</sub>;

Ar is:

5 phenyl, naphthyl, quinoliny, isoquinoliny, tetrahydronaphthyl, tetrahydroquinoliny, tetrahydroisoquinoliny, benzimidazolyl, benzofuranyl, dihydrobenzofuranyl, indoliny, benzothienyl, dihydrobenzothienyl, indanyl, indenyl or indolyl each being optionally substituted by one or more R<sub>4</sub> or R<sub>5</sub>;

10 X is:

a C<sub>5-8</sub> cycloalkyl or cycloalkenyl optionally substituted with one to two oxo groups or one to three C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy or C<sub>1-4</sub> alkylamino chains each being branched or unbranched;

15 aryl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyridinonyl, dihydropyridinonyl, maleimidyl, dihydromaleimidyl, piperdiny, benzimidazole, 3H-imidazo[4,5-b]pyridine, piperazinyl, pyridazinyl or pyrazinyl; each being optionally independently substituted with one to three C<sub>1-4</sub> alkyl, C<sub>1-4</sub>alkoxy, hydroxy, nitrile, amino, mono- or di-(C<sub>1-3</sub> alkyl)amino, mono- or di-(C<sub>1-3</sub> alkylamino)carbonyl, NH<sub>2</sub>C(O), C<sub>1-6</sub>  
20 alkyl-S(O)<sub>m</sub> or halogen;

Y is:

a bond or a C<sub>1-4</sub> saturated or unsaturated branched or unbranched carbon chain optionally  
25 partially or fully halogenated, wherein one or more C atoms are optionally replaced by O, N, or S(O)<sub>m</sub> and wherein Y is optionally independently substituted with one to two oxo groups, nitrile, phenyl or one or more C<sub>1-4</sub> alkyl optionally substituted by one or more halogen atoms;

30 Z is:

aryl, heteroaryl selected from pyridinyl, piperazinyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl and pyranyl, heterocycle selected from tetrahydropyrimidonyl, cyclohexanonyl, cyclohexanolyl, 2-oxa- or 2-thia-5-aza-bicyclo[2.2.1]heptanyl, pentamethylene sulfidyl, pentamethylene sulfoxidyl, pentamethylene sulfonyl, tetramethylene sulfidyl, tetramethylene sulfoxidyl or tetramethylene sulfonyl, tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxolanonyl, 1,3-dioxanonyl, 1,4-dioxanyl, morpholino, thiomorpholino, thiomorpholino sulfoxidyl, thiomorpholino sulfonyl, piperidinyl, piperidinonyl, pyrrolidinyl and dioxolanyl, each of the aforementioned Z are optionally substituted with one to three halogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>1-3</sub> alkoxy-C<sub>1-3</sub> alkyl, C<sub>1-6</sub> alkoxycarbonyl, aroyl, C<sub>1-3</sub> acyl, oxo, hydroxy, pyridinyl-C<sub>1-3</sub> alkyl, imidazolyl-C<sub>1-3</sub> alkyl, tetrahydrofuranyl-C<sub>1-3</sub> alkyl, nitrile-C<sub>1-3</sub> alkyl, nitrile, carboxy, phenyl wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkoxy, hydroxy or mono- or di-(C<sub>1-3</sub> alkyl)amino, C<sub>1-6</sub> alkyl-S(O)<sub>m</sub>, or phenyl-S(O)<sub>m</sub> wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkoxy, hydroxy, halogen or mono- or di-(C<sub>1-3</sub> alkyl)amino; or Z is optionally substituted with one to three amino or amino-C<sub>1-3</sub> alkyl wherein the N atom is optionally independently mono- or di-substituted by aminoC<sub>1-6</sub>alkyl, C<sub>1-3</sub>alkyl, arylC<sub>0-3</sub>alkyl, C<sub>1-5</sub> alkoxyC<sub>1-3</sub> alkyl, C<sub>1-5</sub> alkoxy, aroyl, C<sub>1-3</sub> acyl, C<sub>1-3</sub>alkyl-S(O)<sub>m</sub>- or arylC<sub>0-3</sub>alkyl-S(O)<sub>m</sub>- each of the aforementioned alkyl and aryl attached to the amino group is optionally substituted with one to two halogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy; or Z is optionally substituted with one to three aryl, heterocycle or heteroaryl as hereinabove described in this paragraph each in turn is optionally substituted by halogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy;

or Z is hydroxy, halogen, nitrile, amino wherein the N atom is optionally independently mono- or di-substituted by C<sub>1-3</sub>acyl, C<sub>1-6</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>1-3</sub>alkyl, C<sub>1-6</sub>alkyl branched or unbranched, C<sub>1-6</sub>alkoxy, C<sub>1-3</sub>acylamino, nitrileC<sub>1-4</sub>alkyl, C<sub>1-6</sub> alkyl-S(O)<sub>m</sub>, and phenyl-S(O)<sub>m</sub>, wherein the phenyl ring is optionally substituted with one to two halogen, C<sub>1-6</sub> alkoxy, hydroxy or mono- or di-(C<sub>1-3</sub> alkyl)amino;

each R<sub>1</sub> is independently:

C<sub>1-10</sub> alkyl branched or unbranched optionally partially or fully halogenated, wherein one or more C atoms are optionally independently replaced by O, N or S(O)<sub>m</sub>, and wherein said C<sub>1-10</sub> alkyl is optionally substituted with one to three C<sub>3-10</sub> cycloalkyl, hydroxy, oxo, phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrrolidinyl, imidazolyl, pyrazolyl, thienyl, furyl, dioxolanyl, isoxazolyl or isothiazolyl; each of the aforementioned being optionally substituted with one to five groups selected from halogen, C<sub>1-6</sub> alkyl which is optionally partially or fully halogenated, C<sub>3-8</sub> cycloalkanyl, C<sub>5-8</sub> cycloalkenyl, hydroxy, nitrile, C<sub>1-3</sub> alkoxy which is optionally partially or fully halogenated or NH<sub>2</sub>C(O), mono- or di(C<sub>1-3</sub>alkyl)amino, and mono- or di(C<sub>1-3</sub>alkyl)aminocarbonyl;

or R<sub>1</sub> is cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, or cycloheptyloxy each being optionally partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl groups optionally partially or fully halogenated, nitrile, hydroxyC<sub>1-3</sub>alkyl or aryl; or an analog of such cycloalkyl group wherein one to three ring methylene groups are independently replaced by O, S(O)<sub>m</sub>, CHOH, >C=O, >C=S or NH;

phenyloxy or benzyloxy each being optionally partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl groups optionally partially or fully halogenated, nitrile, hydroxyC<sub>1-3</sub>alkyl or aryl; or an analog of such cycloaryl group wherein one to two ring methyne groups are independently replaced by N;

cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclopentanyl, bicyclohexanyl or bicycloheptanyl, each being optionally partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl optionally partially or fully halogenated, nitrile, hydroxyC<sub>1-3</sub>alkyl or aryl; or an analog of such cycloalkyl group wherein one to three ring methylene groups are independently replaced by O, S(O)<sub>m</sub>, CHOH, >C=O, >C=S or NH;

C<sub>3-10</sub> branched or unbranched alkenyl each being optionally partially or fully halogenated, and optionally substituted with one to three C<sub>1-5</sub> branched or unbranched alkyl, phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl or isothiazolyl, each of the aforementioned being substituted  
5 with one to five halogen, C<sub>1-6</sub> alkyl which is optionally partially or fully halogenated, cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, hydroxy, nitrile, C<sub>1-3</sub> alkyloxy which is optionally partially or fully halogenated, NH<sub>2</sub>C(O), mono- or di(C<sub>1-3</sub>alkyl)aminocarbonyl; the C<sub>3-10</sub> branched or unbranched alkenyl being optionally  
10 interrupted by one or more heteroatoms chosen from O, N and S(O)<sub>m</sub>;

cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl or bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C<sub>1-3</sub> alkyl groups;  
15  
oxo, nitrile, halogen;

silyl containing three C<sub>1-4</sub> alkyl groups optionally partially or fully halogenated; or  
20 C<sub>3-6</sub> alkynyl branched or unbranched carbon chain optionally partially or fully halogenated, wherein one or more methylene groups are optionally replaced by O, NH or S(O)<sub>m</sub> and wherein said alkynyl group is optionally independently substituted with one to two oxo groups, hydroxy, pyrroldinyl, pyrrolyl, tetrahydropyranyl, one or more C<sub>1-4</sub> alkyl optionally substituted by one or more halogen atoms, nitrile, morpholino, piperidinyl,  
25 piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl, or mono- or di(C<sub>1-3</sub>alkyl)amino optionally substituted by one or more halogen atoms;

each R<sub>2</sub>, R<sub>4</sub>, and R<sub>5</sub> is

30 a C<sub>1-6</sub> branched or unbranched alkyl optionally partially or fully halogenated, C<sub>1-6</sub>acyl, aroyl, C<sub>1-4</sub> branched or unbranched alkoxy, each being optionally partially or fully

halogenated, halogen, methoxycarbonyl,  $C_{1-3}$  alkyl-S(O)<sub>m</sub> optionally partially or fully halogenated, or phenyl-S(O)<sub>m</sub>;

OR<sub>6</sub>, C<sub>1-6</sub> alkoxy, hydroxy, nitrile, nitro, halogen;

5

or amino-S(O)<sub>m</sub>- wherein the N atom is optionally independently mono- or di-substituted by C<sub>1-6</sub>alkyl or arylC<sub>0-3</sub>alkyl, or amino wherein the N atom is optionally independently mono- or di-substituted by C<sub>1-3</sub>alkyl, arylC<sub>0-3</sub>alkyl, C<sub>1-6</sub>acyl, C<sub>1-6</sub>alkyl-S(O)<sub>m</sub>- or arylC<sub>0-3</sub>alkyl-S(O)<sub>m</sub>-, each of the aforementioned alkyl and aryl in this subparagraph are  
 10 optionally partially or fully halogenated and optionally substituted with one to two C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy;

each R<sub>3</sub> is independently:

- 15 phenyl, naphthyl, morpholino, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrrolidinyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, [1,3,4]oxadiazol, triazolyl, tetrazolyl, thienyl, furyl, tetrahydrofuryl, isoxazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl,  
 20 quinoxalinyl, quinazolinyl, purinyl or indazolyl, each of the aforementioned is optionally substituted with one to three phenyl, naphthyl, heterocycle or heteroaryl as hereinabove described in this paragraph, C<sub>1-6</sub> branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C<sub>1-5</sub> alkyl,  
 25 naphthyl C<sub>1-5</sub> alkyl, halogen, hydroxy, oxo, nitrile, C<sub>1-3</sub> alkoxy optionally partially or fully halogenated, phenyloxy, naphthyloxy, heteroaryloxy or heterocycloxy wherein the heterocyclic or heteroaryl moiety is as hereinabove described in this paragraph, nitro, amino, mono- or di-(C<sub>1-3</sub>alkyl)amino, phenylamino, naphthylamino, heteroaryl or heterocyclic amino wherein the heteroaryl heterocyclic moiety is as hereinabove  
 30 described in this paragraph, NH<sub>2</sub>C(O), a mono- or di-(C<sub>1-3</sub>alkyl) aminocarbonyl, C<sub>1-5</sub> alkyl-C(O)-C<sub>1-4</sub> alkyl, amino-C<sub>1-5</sub> alkyl, mono- or di-(C<sub>1-5</sub>alkyl)amino, mono- or di-(C<sub>1-</sub>



<sub>3</sub>alkyl)amino-C<sub>1-5</sub> alkyl, amino-S(O)<sub>2</sub>, di-(C<sub>1-3</sub>alkyl)amino-S(O)<sub>2</sub>, R<sub>7</sub>-C<sub>1-5</sub> alkyl, R<sub>8</sub>-C<sub>1-5</sub> alkoxy, R<sub>9</sub>-C(O)-C<sub>1-5</sub> alkyl, R<sub>10</sub>-C<sub>1-5</sub> alkyl(R<sub>11</sub>)N, carboxy-mono- or di-(C<sub>1-5</sub>alkyl)-amino;

a fused aryl selected from benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl, or a fused heteroaryl selected from cyclopentenopyridinyl, cyclohexanopyridinyl, cyclopentanopyrimidinyl, cyclohexanopyrimidinyl, cyclopentanopyrazinyl, cyclohexanopyrazinyl, cyclopentanopyridazinyl, cyclohexanopyridazinyl, cyclopentanoquinolinyl, cyclohexanoquinolinyl, cyclopentanoisoquinolinyl, cyclohexanoisoquinolinyl, cyclopentanoindolyl, cyclohexanoindolyl, cyclopentanobenzimidazolyl, cyclohexanobenzimidazolyl, cyclopentanobenzoxazolyl, cyclohexanobenzoxazolyl, cyclopentanoimidazolyl, cyclohexanoimidazolyl, cyclopentanothienyl and cyclohexanothienyl; wherein the fused aryl or fused heteroaryl ring is independently substituted with zero to three phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, isothiazolyl, C<sub>1-6</sub> alkyl which is optionally partially or fully halogenated, halogen, nitrile, C<sub>1-3</sub> alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heteroaryloxy or heterocycloxy wherein the heteroaryl or heterocyclic moiety is as hereinabove described in this paragraph, nitro, amino, mono- or di-(C<sub>1-3</sub>alkyl)amino, phenylamino, naphthylamino, heteroaryl or heterocyclic amino wherein the heteroaryl or heterocyclic moiety is as hereinabove described in this paragraph, NH<sub>2</sub>C(O), mono- or di-(C<sub>1-3</sub>alkyl)aminocarbonyl, C<sub>1-4</sub> alkyl-OC(O), C<sub>1-5</sub> alkyl-C(O)-C<sub>1-4</sub> alkyl, amino-C<sub>1-5</sub> alkyl, mono- or di-(C<sub>1-3</sub>)alkylamino-C<sub>1-5</sub> alkyl, R<sub>12</sub>-C<sub>1-5</sub> alkyl, R<sub>13</sub>-C<sub>1-5</sub> alkoxy, R<sub>14</sub>-C(O)-C<sub>1-5</sub> alkyl or R<sub>15</sub>-C<sub>1-5</sub> alkyl(R<sub>16</sub>)N;

cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl or bicycloheptanyl, each being optionally be partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl groups, or an analog of such cycloalkyl group wherein one to three ring methylene groups are independently replaced by O, S, CHOH, >C=O, >C=S or NH;

cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl or bicycloheptenyl, each optionally substituted with one to three C<sub>1-3</sub> alkyl groups;

- 5 C<sub>1-4</sub> alkyl-phenyl-C(O)-C<sub>1-4</sub> alkyl-, C<sub>1-4</sub> alkyl-C(O)-C<sub>1-4</sub> alkyl- or C<sub>1-4</sub> alkyl-phenyl-S(O)<sub>m</sub>-C<sub>1-4</sub> alkyl-;

C<sub>1-6</sub> alkyl or C<sub>1-6</sub> branched or unbranched alkoxy each of which is optionally partially or fully halogenated or optionally substituted with R<sub>17</sub>;

10

OR<sub>18</sub> or C<sub>1-6</sub> alkyl optionally substituted with OR<sub>18</sub>;

amino or mono- or di-(C<sub>1-5</sub>alkyl)amino optionally substituted with R<sub>19</sub>;

- 15 R<sub>20</sub>C(O)N(R<sub>21</sub>)-, R<sub>22</sub>O- or R<sub>23</sub>R<sub>24</sub>NC(O)-; R<sub>26</sub>(CH<sub>2</sub>)<sub>m</sub>C(O)N(R<sub>21</sub>)-, R<sub>23</sub>R<sub>24</sub>NC(O)-C<sub>1-3</sub>alkoxy or R<sub>26</sub>C(O)(CH<sub>2</sub>)<sub>m</sub>N(R<sub>21</sub>)-;

C<sub>2-6</sub>alkenyl substituted by R<sub>23</sub>R<sub>24</sub>NC(O)-;

- 20 C<sub>2-6</sub> alkynyl branched or unbranched carbon chain, optionally partially or fully halogenated, wherein one or more methylene groups are optionally replaced by O, NH, S(O)<sub>m</sub> and wherein said alkynyl group is optionally independently substituted with one to two oxo groups, pyrrolidinyl, pyrrolyl, morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl one or more C<sub>1-4</sub> alkyl optionally substituted by one or more  
 25 halogen atoms, nitrile, morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl, or mono- or di-(C<sub>1-4</sub> alkyl)amino optionally substituted by one or more halogen atoms;

C<sub>1-6</sub>acyl or aroyl;

30

R<sub>6</sub> is a:

C<sub>1-4</sub> alkyl optionally partially or fully halogenated and optionally substituted with R<sub>26</sub>;

each R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, R<sub>12</sub>, R<sub>13</sub>, R<sub>14</sub>, R<sub>15</sub>, R<sub>17</sub>, R<sub>19</sub>, R<sub>25</sub> and R<sub>26</sub> is independently:

5 nitrile, phenyl, morpholino, piperidinyl, piperazinyl, imidazolyl, pyridinyl, tetrazolyl,  
amino or mono- or di-(C<sub>1-4</sub>alkyl)amino optionally partially or fully halogenated;

each R<sub>11</sub> and R<sub>16</sub> is independently:

hydrogen or C<sub>1-4</sub> alkyl optionally partially or fully halogenated;

10

R<sub>18</sub> is independently:

hydrogen or a C<sub>1-4</sub> alkyl optionally independently substituted with oxo or R<sub>25</sub>;

R<sub>20</sub> is independently:

15 C<sub>1-10</sub> alkyl optionally partially or fully halogenated, phenyl, or pyridinyl;

R<sub>21</sub> is independently:

hydrogen or C<sub>1-3</sub> alkyl optionally partially or fully halogenated;

20 each R<sub>22</sub>, R<sub>23</sub> and R<sub>24</sub> is independently:

hydrogen, C<sub>1-6</sub> alkyl optionally partially or fully halogenated, said C<sub>1-6</sub> alkyl is optionally interrupted by one or more O, N or S, said C<sub>1-6</sub> alkyl also being independently optionally substituted by mono- or di-(C<sub>1-3</sub>alkyl)aminocarbonyl, phenyl, pyridinyl, amino or mono- or di-(C<sub>1-4</sub>alkyl)amino each of which is optionally partially or fully halogenated and

25 optionally substituted with mono- or di-(C<sub>1-3</sub>alkyl)amino;

or R<sub>23</sub> and R<sub>24</sub> taken together optionally form a heterocyclic or heteroaryl ring;

m = 0, 1 or 2;

30 W is O or S and

the pharmaceutically acceptable derivatives thereof.

2. The method according to claim 1 wherein

E is -CH<sub>2</sub>-, -NH- or -O-;

5 W is O;

and

G is:

phenyl, naphthyl, benzocyclobutanyl, dihydronaphthyl, tetrahydronaphthyl,

10 benzocycloheptanyl, benzocycloheptenyl, indanyl, indenyl;

pyridinyl, pyridonyl, quinolinyl, dihydroquinolinyl, tetrahydroquinoyl, isoquinolinyl,  
tetrahydroisoquinoyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzimidazolyl, benzthiazolyl,  
benzooxazolyl, benzofuranyl, benzothiophenyl, benzpyrazolyl, dihydrobenzofuranyl,  
15 dibenzofuranyl, dihydrobenzothiophenyl, benzooxazolonyl, benzo[1,4]oxazin-3-onyl,  
benzodioxolyl, benzo[1,3]dioxol-2-onyl, benzofuran-3-onyl, tetrahydrobenzopyranyl,  
indolyl, 2,3-dihydro-1H-indolyl, indolinyl, indolonyl, indolinonyl, phthalimidyl,  
chromoyl;

oxetanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, piperidinyl, piperazinyl,  
20 morpholino, tetrahydropyranyl, dioxanyl, tetramethylene sulfonyl, tetramethylene  
sulfoxidyl, oxazoliny, 3,4-dihydro-2H-benzo[1,4]oxazinyl, thiazoliny, imidazoliny,  
tetrahydropyridiny, homopiperidinyl, pyrroliny, tetrahydropyrimidinyl,  
decahydroquinolinyl, decahydroisoquinolinyl, thiomorpholino, thiazolidinyl,  
dihydrooxazinyl, dihydropyranyl, oxocanyl, heptacanyl, thioxanyl or dithianyl;

25 wherein G is optionally substituted by one or more R<sub>1</sub>, R<sub>2</sub> or R<sub>3</sub>.

3. The method according to claim 2 wherein

30 E is -NH-;

G is phenyl, pyridinyl, pyridonyl, naphthyl, quinolinyl, isoquinolinyl, pyrazinyl, benzimidazolyl, benzooxazolyl, benzooxazolonyl, benzofuranyl, benzothiophenyl, benzpyrazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, 3,4-dihydro-2H-benzo[1,4]oxazinyl, indanyl, indenyl, indolyl, indolinyl, indolonyl, 2,3-dihydro-1H-indolyl or indolinonyl, wherein G is optionally substituted by one or more R<sub>1</sub>, R<sub>2</sub> or R<sub>3</sub>;

Ar is:

naphthyl, quinolinyl, isoquinolinyl, tetrahydronaphthyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, indanyl, indenyl or indolyl each being optionally substituted by one or more R<sub>4</sub> or R<sub>5</sub> groups;

X is:

phenyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyridinonyl, dihydropyridinonyl, maleimidyl, dihydromaleimidyl, piperdinyl, piperazinyl, pyridazinyl or pyrazinyl; each being optionally independently substituted with one to three C<sub>1-4</sub> alkyl, C<sub>1-4</sub>alkoxy, hydroxy, nitrile, amino, mono- or di-(C<sub>1-3</sub> alkyl)amino, mono- or di-(C<sub>1-3</sub> alkylamino)carbonyl, NH<sub>2</sub>C(O), C<sub>1-6</sub> alkyl-S(O)<sub>m</sub> or halogen;

Y is:

a bond or

a C<sub>1-4</sub> saturated or unsaturated carbon chain wherein one or more of the C atoms is optionally replaced by O, N, or S(O)<sub>m</sub> and wherein Y is optionally independently substituted with one to two oxo groups, nitrile, phenyl or one or more C<sub>1-4</sub> alkyl optionally substituted by one or more halogen atoms;

Z is:

phenyl, heteroaryl selected from pyridinyl, piperazinyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, furanyl, thienyl and pyranyl, heterocycle selected from 2-oxa-5-aza-bicyclo[2.2.1]heptanyl, tetrahydropyrimidinyl, pentamethylene sulfidyl, pentamethylene sulfoxidyl, pentamethylene sulfonyl, tetramethylene sulfidyl, tetramethylene sulfoxidyl tetramethylene sulfonyl, tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxolanonyl, 1,3-dioxanonyl, 1,4-dioxanyl, morpholino, thiomorpholino, thiomorpholino sulfoxidyl, piperidinyl, piperidinonyl, dihydrothiazolyl, dihydrothiazolyl sulfoxidyl, pyrrolidinyl and dioxolanyl which are optionally substituted with one to three nitrile, C<sub>1-3</sub> alkyl, C<sub>1-3</sub> alkoxy, amino, mono- or di-(C<sub>1-3</sub> alkyl)amino, CONH<sub>2</sub> or OH;  
or Z is optionally substituted by phenyl, heterocycle or heteroaryl as hereinabove described in this paragraph each in turn is optionally substituted by halogen, C<sub>1-3</sub> alkyl or C<sub>1-3</sub> alkoxy;

or Z is nitrile, nitrileC<sub>1-3</sub> alkyl, C<sub>1-6</sub> alkyl-S(O)<sub>m</sub>, halogen, hydroxy, C<sub>1-3</sub> alkyl, C<sub>1-3</sub> acylamino, C<sub>1-4</sub> alkoxy, amino, mono- or di-(C<sub>1-3</sub> alkyl)aminocarbonyl, or amino mono or di-substituted by aminoC<sub>1-6</sub> alkyl or C<sub>1-3</sub>alkoxyC<sub>1-3</sub>alkyl;

each R<sub>1</sub> is independently:

C<sub>1-6</sub> alkyl branched or unbranched optionally partially or fully halogenated, wherein one or more C atoms are optionally independently replaced by O, N or S(O)<sub>m</sub>, and wherein said C<sub>1-6</sub> alkyl is optionally substituted with one to three C<sub>3-6</sub>cycloalkyl, oxo, phenyl, dioxolanyl, pyrrolidinyl, furyl, isoxazolyl or isothiazolyl; each of the aforementioned being optionally substituted with one to three groups selected from halogen, C<sub>1-3</sub> alkyl which is optionally partially or fully halogenated, hydroxy, nitrile and C<sub>1-3</sub>alkoxy which is optionally partially or fully halogenated;

cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, bicyclopentanyl or bicyclohexanyl, each being optionally partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl groups optionally partially or fully halogenated, nitrile, hydroxyC<sub>1-3</sub>alkyl

or phenyl; or an analog of such cycloalkyl group wherein one to three ring methylene groups are independently replaced by O, S, CHOH,  $>C=O$ ,  $>C=S$  or NH;

oxo;

5

$C_{3-6}$  alkynyl branched or unbranched carbon chain optionally partially or fully halogenated, wherein one or more methylene groups are optionally replaced by O, NH or  $S(O)_m$  and wherein said alkynyl group is optionally independently substituted with one to two oxo groups, hydroxy, pyrroldinyl, pyrrolyl, tetrahydropyranyl,  $C_{1-4}$  alkyl optionally substituted by one or more halogen atoms, nitrile, morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl, or mono- or di( $C_{1-3}$ alkyl)amino optionally substituted by one or more halogen atoms;

10

or

15

silyl containing three  $C_{1-4}$  alkyl groups optionally partially or fully halogenated;

$R_2$  is independently:

20

a  $C_{1-5}$  branched or unbranched alkyl optionally partially or fully halogenated, acetyl, aroyl,  $C_{1-4}$  branched or unbranched alkoxy, each being optionally partially or fully halogenated, halogen, methoxycarbonyl,  $C_{1-2}$  alkyl- $S(O)_m$  optionally partially or fully halogenated, or phenyl- $S(O)_m$ ;

25

$C_{1-3}$  alkoxy, hydroxy, nitrile, nitro, halogen;

30

or amino- $S(O)_m$ - wherein the N atom is optionally independently mono- or di-substituted by  $C_{1-3}$ alkyl or aryl $C_{0-3}$ alkyl, or amino wherein the N atom is optionally independently mono- or di-substituted by  $C_{1-3}$ alkyl, aryl $C_{0-3}$ alkyl,  $C_{1-3}$ acyl,  $C_{1-4}$ alkyl- $S(O)_m$ - or aryl $C_{0-3}$ alkyl- $S(O)_m$ -, each of the aforementioned alkyl and aryl in this subparagraph are optionally partially or fully halogenated and optionally substituted with one to two  $C_{1-3}$  alkyl or  $C_{1-3}$  alkoxy;

R<sub>3</sub> is independently:

- phenyl, morpholino, pyridinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrrolidinyl, imidazolyl,  
 5 [1,3,4]oxadiazol, pyrazolyl, each is optionally substituted with one to three phenyl,  
 naphthyl, heterocycle or heteroaryl as hereinabove described in this paragraph, C<sub>1-6</sub> alkyl  
 which is optionally partially or fully halogenated, cyclopropanyl, cyclobutanyl,  
 cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl,  
 bicycloheptanyl, phenyl C<sub>1-5</sub> alkyl, naphthyl C<sub>1-5</sub> alkyl, halogen, oxo, hydroxy, nitrile, C<sub>1-3</sub>  
 10 alkoxy optionally partially or fully halogenated, phenyloxy, naphthyloxy, heteroaryloxy  
 or heterocycloxy wherein the heteroaryl or heterocyclic moiety is as hereinabove  
 described in this paragraph, nitro, amino, mono- or di-(C<sub>1-3</sub>alkyl)amino, phenylamino,  
 naphthylamino, heteroaryl or heterocyclic amino wherein the heteroaryl or heterocyclic  
 moiety is as hereinabove described in this paragraph, NH<sub>2</sub>C(O), a mono- or di-(C<sub>1-3</sub>  
 15 alkyl)aminocarbonyl, C<sub>1-5</sub> alkyl-C(O)-C<sub>1-4</sub> alkyl, mono- or di-(C<sub>1-3</sub>alkyl)amino, mono- or  
 di-(C<sub>1-3</sub>)alkylamino-C<sub>1-5</sub> alkyl, mono- or di-(C<sub>1-3</sub>alkyl)amino-S(O)<sub>2</sub>, R<sub>7</sub>-C<sub>1-5</sub> alkyl, R<sub>8</sub>-C<sub>1-5</sub>  
 alkoxy, R<sub>9</sub>-C(O)-C<sub>1-5</sub> alkyl, R<sub>10</sub>-C<sub>1-5</sub> alkyl(R<sub>11</sub>)N, carboxy-mono- or di-(C<sub>1-5</sub>)-alkyl-  
 amino;  
 20 C<sub>1-3</sub> alkyl or C<sub>1-4</sub> alkoxy each being optionally partially or fully halogenated or optionally  
 substituted with R<sub>17</sub>;

OR<sub>18</sub> or C<sub>1-6</sub> alkyl optionally substituted with OR<sub>18</sub>;

- 25 amino or mono- or di- (C<sub>1-5</sub> alkyl)amino optionally substituted with R<sub>19</sub>;

R<sub>20</sub>C(O)N(R<sub>21</sub>)-, R<sub>22</sub>O- ; R<sub>23</sub>R<sub>24</sub>NC(O)-; R<sub>26</sub>CH<sub>2</sub>C(O)N(R<sub>21</sub>)-, R<sub>23</sub>R<sub>24</sub>NC(O)-C<sub>1-2</sub>alkoxy  
 or R<sub>26</sub>C(O)CH<sub>2</sub>N(R<sub>21</sub>)-;

- 30 C<sub>2-4</sub>alkenyl substituted by R<sub>23</sub>R<sub>24</sub>NC(O)-; or



C<sub>2-4</sub> alkynyl branched or unbranched carbon chain optionally partially or fully halogenated wherein one of the methylene groups is optionally replaced by O, and optionally independently substituted with one to two oxo groups, pyrroldinyl, pyrrolyl, morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl or one or more C<sub>1-4</sub> alkyl optionally substituted by one or more halogen atoms;

C<sub>1-3</sub>acyl; and

R<sub>23</sub> and R<sub>24</sub> taken together optionally form imidazolyl, piperidinyl, morpholino, piperazinyl or a pyridinyl ring.

4. The method according to claim 3 wherein:

G is phenyl, pyridinyl, pyridonyl, naphthyl, quinolinyl, isoquinolinyl, pyrazinyl, 3,4-dihydro-2H-benzo[1,4]oxazinyl, benzothiophenyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, benzooxazolyl, indanyl, indolyl, indolinyl, indolonyl or indolinonyl, wherein G is optionally substituted by one or more R<sub>1</sub>, R<sub>2</sub> or R<sub>3</sub>;

Ar is naphthyl;

X is

phenyl, imidazolyl, pyridinyl, pyrimidinyl, piperdinyl, piperazinyl, pyridazinyl or pyrazinyl each being optionally independently substituted with one to three C<sub>1-4</sub> alkyl, C<sub>1-4</sub>alkoxy, hydroxy, nitrile, amino, mono- or di-(C<sub>1-3</sub> alkyl)amino, mono- or di-(C<sub>1-3</sub> alkylamino)carbonyl, NH<sub>2</sub>C(O), C<sub>1-6</sub> alkyl-S(O)<sub>m</sub> or halogen;

Y is:

a bond or

a C<sub>1-4</sub> saturated carbon chain wherein one or more of the C atoms is optionally replaced by O, N or S and wherein Y is optionally independently substituted with nitrile or oxo;

Z is:

phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, dihydrothiazolyl, dihydrothiazolyl sulfoxide, pyranyl, pyrrolidinyl, phenylpiperazinyl, tetrahydropyranyl, 5 tetrahydrofuranyl, dioxolanyl, 2-oxa-5-aza-bicyclo[2.2.1]heptanyl, morpholino, thiomorpholino, thiomorpholino sulfoxidyl, piperidinyl, piperidinonyl, piperazinyl or tetrahydropyrimidonyl each of which are optionally substituted with one to two C<sub>1-2</sub> alkyl or C<sub>1-2</sub> alkoxy; or

- 10 Z is hydroxy, C<sub>1-3</sub> alkyl, C<sub>1-3</sub> alkoxy, C<sub>1-3</sub> acylamino, C<sub>1-3</sub> alkylsulfonyl, nitrile C<sub>1-3</sub> alkyl or amino mono or di-substituted by C<sub>1-3</sub> alkoxyC<sub>1-3</sub> alkyl;

each R<sub>1</sub> is independently:

- 15 C<sub>1-5</sub> alkyl branched or unbranched optionally partially or fully halogenated, wherein one or more C atoms are optionally independently replaced by O, N or S(O)<sub>m</sub>, and wherein said C<sub>1-5</sub> alkyl is optionally substituted with oxo, dioxolanyl, pyrrolidinyl, furyl or phenyl each optionally substituted with one to three halogen, C<sub>1-3</sub> alkyl which is optionally partially or fully halogenated, hydroxy, nitrile and C<sub>1-3</sub>alkoxy which is 20 optionally partially or fully halogenated;

cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, bicyclopentanyl or bicyclohexanyl, each being optionally partially or fully halogenated and optionally substituted with one to three C<sub>1-3</sub> alkyl groups optionally partially or fully halogenated, nitrile, hydroxyC<sub>1-3</sub>alkyl 25 or phenyl; and an analog of cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, bicyclopentanyl or bicyclohexanyl wherein one ring methylene group is replaced by O;

oxo;

- 30 C<sub>2-4</sub> alkynyl optionally partially or fully halogenated wherein one or more methylene groups are optionally replaced by O, and optionally independently substituted with one to

two oxo groups, hydroxy, pyrroldinyl, pyrrolyl, tetrahydropyranyl, C<sub>1-4</sub> alkyl optionally substituted by one or more halogen atoms, nitrile, morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl, or mono- or di(C<sub>1-3</sub>alkyl)amino optionally substituted by one or more halogen atoms;

5

or

silyl containing three C<sub>1-2</sub> alkyl groups optionally partially or fully halogenated;

10

each R<sub>2</sub> is independently:

a C<sub>1-4</sub> alkyl optionally partially or fully halogenated, C<sub>1-4</sub> alkoxy optionally partially or fully halogenated, bromo, chloro, fluoro, methoxycarbonyl, methyl-S(O)<sub>m</sub>, ethyl-S(O)<sub>m</sub> each optionally partially or fully halogenated or phenyl-S(O)<sub>m</sub>;

15

or R<sub>2</sub> is mono- or di-C<sub>1-3</sub>acylamino, amino-S(O)<sub>m</sub> or S(O)<sub>m</sub>amino wherein the N atom is mono- or di-substituted by C<sub>1-3</sub>alkyl or phenyl, nitrile, nitro or amino;

each R<sub>3</sub> is independently:

20

phenyl, morpholino, pyridinyl, pyrimidinyl, pyrrolidinyl, 2,5-pyrrolidin-dionyl, imidazolyl, [1,3,4]oxadiazol, pyrazolyl, each of the aforementioned is optionally substituted with one to three C<sub>1-3</sub> alkyl which is optionally partially or fully halogenated, halogen, oxo, hydroxy, nitrile and C<sub>1-3</sub> alkoxy optionally partially or fully halogenated;

25

C<sub>1-3</sub> alkyl or C<sub>1-3</sub> alkoxy optionally partially or fully halogenated or optionally substituted with R<sub>17</sub>;

OR<sub>18</sub> or C<sub>1-3</sub> alkyl optionally substituted with OR<sub>18</sub>;

amino or mono- or di-(C<sub>1-3</sub> alkyl)amino optionally substituted with R<sub>19</sub>;

30

$R_{20}C(O)N(R_{21})-$ ,  $R_{22}O-$ ;  $R_{23}R_{24}NC(O)-$ ;  $R_{26}CH_2C(O)N(R_{21})-$ ,  $NH_2C(O)$ methoxy or  $R_{26}C(O)CH_2N(R_{21})-$ ;

$C_{2-4}$  alkenyl substituted by  $R_{23}R_{24}NC(O)-$ ; or

5

$C_{2-4}$  alkynyl substituted with pyrrolidinyl or pyrrolyl;

$C_{1-3}$ acyl and

10  $R_{23}$  and  $R_{24}$  taken together optionally form morpholino.

5. The method according to claim 4 wherein

15 G is phenyl, pyridinyl, pyridonyl, 2-naphthyl, quinolinyl, isoquinolinyl, dihydrobenzofuranyl, indanyl, 5-indolyl, 3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl, benzooxalolyl, 2,3-dihydrobenzooxazol-7-yl, 2-oxo-2,3-dihydro-1H-indol-5-yl, indolinyl, indolonyl, or indolinonyl, wherein G is optionally substituted by one or more  $R_1$ ,  $R_2$  or  $R_3$ ;

20

Ar is 1-naphthyl;

X is:

25 phenyl, imidazolyl, pyridinyl, pyrimidinyl, piperdinyl, piperazinyl, pyridazinyl or pyrazinyl;

Y is:

a bond or

30  $-CH_2-$ ,  $-CH_2CH_2-$ ,  $-C(O)-$ ,  $-O-$ ,  $-S-$ ,  $-NH-CH_2CH_2CH_2-$ ,  $-N(CH_3)-$ ,  $CH_2(CN)CH_2-NH-CH_2$  or  $-NH-$ ;

Z is

- morpholino, dioxolanyl, tetrahydrofuranyl, pyridinyl, 2-oxa-5-aza-bicyclo[2.2.1]heptanyl,  
5 C<sub>1-3</sub>alkoxyphenylpiperazinyl, hydroxy, C<sub>1-3</sub>alkyl,  
N,N-diC<sub>1-3</sub>alkoxyC<sub>1-3</sub>alkylamino, C<sub>1-3</sub>acylamino, C<sub>1-3</sub>alkylsulfonyl or nitrileC<sub>1-3</sub>alkyl;

each R<sub>1</sub> is independently:

- 10 C<sub>1-5</sub> alkyl optionally partially or fully halogenated wherein one or more C atoms are  
optionally independently replaced by O or N, and wherein said C<sub>1-5</sub> alkyl is optionally  
substituted with oxo, dioxolanyl, pyrrolidinyl, furyl or phenyl optionally substituted by  
C<sub>1-3</sub>alkoxy;  
15 cyclopropyl, cyclopentanyl, cyclohexanyl and bicyclopentanyl optionally substituted with  
one to three methyl groups optionally partially or fully halogenated, nitrile,  
hydroxymethyl or phenyl; or 2-tetrahydrofuranyl substituted by methyl; or  
trimethyl silyl;  
20 propynyl substituted hydroxy or tetrahydropyran-2-yloxy;

R<sub>2</sub> is

- is mono- or di-C<sub>1-3</sub>acylamino, amino-S(O)<sub>m</sub> or S(O)<sub>m</sub> amino wherein the N atom is mono-  
or di-substituted by C<sub>1-3</sub>alkyl or phenyl, bromo, chloro, fluoro, nitrile, nitro, amino,  
25 methylsulfonyl optionally partially or fully halogenated or phenylsulfonyl;

each R<sub>3</sub> is independently:

- phenyl, morpholino, pyridinyl, pyrimidinyl, pyrrolidinyl, 2,5-pyrrolidin-dionyl,  
30 imidazolyl, [1,3,4]oxadiazol or pyrazolyl, each is optionally substituted with C<sub>1-2</sub> alkyl  
which is optionally partially or fully halogenated;

C<sub>1-3</sub> alkyl or C<sub>1-3</sub> alkoxy each being optionally partially or fully halogenated or optionally substituted with diethylamino;

OR<sub>18</sub> or C<sub>1-3</sub> alkyl optionally substituted with OR<sub>18</sub>;

5

amino or mono- or di-(C<sub>1-3</sub> alkyl)amino optionally substituted with R<sub>19</sub>;

CH<sub>3</sub>C(O)NH-, R<sub>22</sub>O-; R<sub>23</sub>R<sub>24</sub>NC(O)-; R<sub>26</sub>CH<sub>2</sub>C(O)N(R<sub>21</sub>)-, NH<sub>2</sub>C(O)methoxy or R<sub>26</sub>C(O)CH<sub>2</sub>N(R<sub>21</sub>)-;

10

C<sub>2-4</sub>alkenyl substituted by R<sub>23</sub>R<sub>24</sub>NC(O)-; or

C<sub>2-4</sub> alkynyl substituted with pyrrolidiny or pyrrolyl;

15

C<sub>1-2</sub>acyl; and

R<sub>23</sub> and R<sub>24</sub> are H or R<sub>23</sub> and R<sub>24</sub> taken together optionally form morpholino; and

R<sub>26</sub> is morpholino.

20

6. The method according to claim 5 wherein

G is

25

phenyl, pyridinyl, 5-indolyl, 3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl, benzoxalolyl, 2,3-dihydrobenzooxazol-7-yl, 2-oxo-2,3-dihydro-1H-indol-5-yl or 2-naphthyl wherein G is optionally substituted by one or more R<sub>1</sub>, R<sub>2</sub> or R<sub>3</sub>;

X is:

30

imidazolyl, pyridinyl, pyrimidinyl or pyrazinyl;

Y is:

a bond,  $\text{CH}_2(\text{CN})\text{CH}_2\text{-NH-CH}_2$ ,  $-\text{CH}_2-$ ,  $-\text{NH-CH}_2\text{CH}_2\text{CH}_2-$  or  $-\text{NH-}$ ;

Z is morpholin-4-yl, dioxolan-2-yl, tetrahydrofuranyl, pyridinyl, 2-oxa-5-aza-  
5 bicyclo[2.2.1]hept-5-yl, methoxyphenylpiperazinyl, hydroxy, methyl, N,N-  
dimethoxyethylamino, acetylamino, methylsulfonyl or cyanoethyl;

each  $\text{R}_1$  is independently:

tert-butyl, sec-butyl, tert-amyl, phenyl, tetrahydropyran-2-yloxypropynyl,  
10 hydroxypropynyl, trihalomethyl, 2,2-diethylpropionyl or cyclohexanyl;

$\text{R}_2$  is chloro, nitro, amino, nitrile, methylsulfonylamino, diacetylamino,  
phenylsulfonylamino, N,N-di(methylsulfonyl)amino, methylsulfonyl or  
trihalomethylsulfonyl;

15

$\text{R}_3$  is independently:

methyl,  $\text{C}_{1-3}$  alkoxy, methoxymethyl, hydroxypropyl, dimethylamino,  $\text{C}_{1-4}$ alkylamino,  
 $\text{NH}_2\text{C(O) methoxy}$ , acetyl, pyrrolidinyl, imidazolyl, pyrazolyl, morpholino or  
20 morpholinocarbonyl.

7. The method according to claim 6 wherein

25 X is pyridinyl.

8. The method according to claim 7 wherein

the pyridinyl is attached to Ar via the 3-pyridinyl position.

30

9. A method of treating a cytokine mediated disease or condition chosen from: acute and chronic inflammation in the lung caused by inhalation of smoke, endometriosis, Behcet's disease, uveitis, ankylosing spondylitis, pancreatitis, cancer, Lyme disease, restenosis following percutaneous transluminal coronary angioplasty, traumatic arthritis, sepsis, chronic obstructive pulmonary disease and congestive heart failure, said method comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound chosen from:

1-(4-tert-Butyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methyl-phenyl)-3-[4-(4-morpholin-4-ylmethyl-piperidin-1-yl)-naphthalen-1-yl]-urea;

1-(6-Chloro-4-trifluoromethyl-pyridin-2-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(4-Difluoromethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(3-Methyl-naphthalen-2-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[2-Methoxy-5-(1-methyl-1-phenyl-ethyl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

(5-tert-Butyl-2-methyl-phenyl)-carbamic acid 3-(5-{4-[3-(5-tert-butyl-2-methyl-phenyl)-ureido]-naphthalen-1-yl}-pyridin-2-ylamino)-propyl ester;

1-(6-tert-Butyl-benzo[1,3]dioxol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-acetamide;

1,3-Bis-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-3-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-2-hydroxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;



1-[5-tert-Butyl-3-(2,3-dihydroxy-propyl)-2-hydroxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

5 1-(2,3-Dimethyl-1H-indol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(2-p-tolyloxy-5-trifluoromethyl-phenyl)-urea;

10 1-[2-(2-Methoxy-phenoxy)-5-trifluoromethyl-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-naphthalen-1-yl-urea;

15 1-{5-tert-Butyl-2-methyl-3-[3-(tetrahydro-pyran-2-yloxy)-prop-1-ynyl]-phenyl}-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

20 1-{5-tert-Butyl-2-[3-(tetrahydro-pyran-2-yloxy)-prop-1-ynyl]-phenyl}-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-Hydroxymethyl-2-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

25 1-(2-Methoxy-dibenzofuran-3-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2,5-Di-tert-butyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

30 1-[3-(4-Bromo-1-methyl-1H-pyrazol-3-yl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(3-Hydroxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

35 1-(1-Acetyl-2,3-dihydro-1H-indol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

40 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(3-oxazol-5-yl-phenyl)-urea;

1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(3-[1,3,4]oxadiazol-2-yl-phenyl)-urea;

45 1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

Furan-2-carboxylic acid (4-tert-butyl-2-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-amide;

5 1-(2-Methoxy-4-phenylamino-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-Methoxy-2-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

10 1-(3-Hydroxy-naphthalen-2-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

15 N,N-Diethyl-4-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-benzenesulfonamide;

1-(2,2-Difluoro-benzo[1,3]dioxol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

20 1-[5-(1,1-Dimethyl-propyl)-2-phenoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-(2,2-Dimethyl-propionyl)-2-methyl-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

25 2-Chloro-5-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-benzoic acid isopropyl ester;

30 1-(4-Amino-3,5-dibromo-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-3-(3-hydroxy-prop-1-ynyl)-2-methyl-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

35 1-[5-tert-Butyl-2-(3-hydroxy-prop-1-ynyl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-3-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

40 1-[5-tert-Butyl-3-(2,3-dihydroxy-propyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

45 1-(5-tert-Butoxy-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-(1-Cyano-cyclopropyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

5 1-[5-tert-Butyl-3-(2-diethylamino-ethyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-[1,3]dioxolan-2-yl-pyridin-3-yl)-naphthalen-1-yl]-urea;

10 1-(5-tert-Butyl-2-pyrrolidin-1-yl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-dimethylamino-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

15 1-(5-tert-Butyl-2-propoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

20 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-hydroxymethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2,6-dimethyl-morpholin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

25 2-(5-tert-Butyl-2-methoxy-phenyl)-N-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-acetamide;

1-(2-Methoxy-5-phenoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

30 1-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-7-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

35 1-(5-tert-Butyl-2-cyclopentyloxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(3-pyridin-3-yl-pyrrolidin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

40 1-(5-Cyclohexyl-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2,4-Dimethoxy-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

45 1-(6-tert-Butyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-3-[4-(6-morpholin-4-

ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-3-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

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1-(3-Amino-5-tert-butyl-2-methoxy-phenyl)-3-[4-(6-methyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

10 N-Acetyl-N-(5-tert-butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-acetamide;

1-(6-tert-Butyl-4-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

15 1-[6-tert-Butyl-4-(2-morpholin-4-yl-ethyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-ethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

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1-(5-tert-Butyl-2-isopropoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

25 1-(5-tert-Butyl-2-imidazol-1-yl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

N-(5-tert-Butyl-2-methoxy-4-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-methanesulfonamide;

30 1-(5-tert-Butyl-3-ethylamino-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-bis(methanesulfon)amide;

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1-[5-tert-Butyl-2-(1-methyl-1H-pyrazol-4-yl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

40 1-(2-Methanesulfinyl-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2-Ethanesulfonyl-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

45 1-[4-(6-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-pyridin-3-yl)-naphthalen-1-yl]-3-(5-tert-butyl-2-methoxy-phenyl)-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(3-dimethylamino-pyrrolidin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

5 N-[1-(5-{4-[3-(5-tert-Butyl-2-methoxy-phenyl)-ureido]-naphthalen-1-yl}-pyridin-2-ylmethyl)-pyrrolidin-3-yl]-acetamide;

1-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

10 N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-propionamide;

15 1-(5-tert-Butyl-2-methyl-benzooxazol-7-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(3-trifluoromethanesulfonyl-phenyl)-urea;

20 N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-isobutyramide;

25 2-(4-tert-Butyl-2-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenoxy)-acetamide;

1-(5-tert-Butyl-2-oxo-2,3-dihydro-benzooxazol-7-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

30 1-(6-tert-Butyl-3-cyano-2-methoxymethoxy-pyridin-4-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(6-tert-Butyl-3-cyano-2-hydroxy-pyridin-4-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

35 1-(5-tert-Butyl-3-cyano-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(1,3,3-trimethyl-2,3-dihydro-1H-indol-5-yl)-urea;

40 1-(5-tert-Butyl-benzooxazol-7-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

45 N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-benzenesulfonamide;

Ethanesulfonic acid (5-tert-butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-amide;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(4-morpholin-4-ylmethyl-piperidin-1-yl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-2-(1-methyl-1H-pyrazol-4-yl)-phenyl]-3-[4-(4-morpholin-4-ylmethyl-piperidin-1-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(2-morpholin-4-ylmethyl-pyrimidin-5-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methylsulfanyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-pyridin-3-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

2,2,2-Trifluoro-ethanesulfonic acid (5-tert-butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-amide;

N-(5-{4-[3-(5-tert-Butyl-2-methyl-phenyl)-ureido]-naphthalen-1-yl}-pyrazin-2-yl)-methanesulfonamide;

1-[4-(6-{[Bis-(2-cyano-ethyl)-amino]-methyl}-pyridin-3-yl)-naphthalen-1-yl]-3-(5-tert-butyl-2-methoxy-phenyl)-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-thiomorpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2,6-dimethyl-piperidin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(1-oxo-tetrahydro-thiopyran-4-ylamino)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(tetrahydro-pyran-4-ylamino)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-{[(2-cyano-ethyl)-(tetrahydro-furan-2-ylmethyl)-amino]-methyl}-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2-methoxymethyl-morpholin-4-ylmethyl)-

pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-(4-{6-[(2-morpholin-4-yl-ethylamino)-methyl]-pyridin-3-yl}-naphthalen-1-yl)-urea;

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1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2-methyl-3-oxo-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

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1-(5-{4-[3-(5-tert-Butyl-2-methoxy-phenyl)-ureido]-naphthalen-1-yl}-pyridin-2-ylmethyl)-piperidine-3-carboxylic acid amide;

1-(5-{4-[3-(5-tert-Butyl-2-methoxy-phenyl)-ureido]-naphthalen-1-yl}-pyridin-2-ylmethyl)-piperidine-4-carboxylic acid amide;

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1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(1-oxo-1,4-thiomorpholin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

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1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(3-oxo-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

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1-{4-[6-(4-Acetyl-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-3-(5-tert-butyl-2-methoxy-phenyl)-urea;

4-(5-{4-[3-(5-tert-Butyl-2-methoxy-phenyl)-ureido]-naphthalen-1-yl}-pyridin-2-ylmethyl)-piperazine-1-carboxylic acid ethyl ester;

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1-(5-tert-Butyl-2-methoxy-phenyl)-3-(4-{6-[(2-pyridin-3-yl-ethylamino)-methyl]-pyridin-3-yl}-naphthalen-1-yl)-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-(4-{6-[(tetrahydro-furan-3-ylamino)-methyl]-pyridin-3-yl}-naphthalen-1-yl)-urea;

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1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-{[(2-cyano-ethyl)-pyridin-3-ylmethyl-amino]-methyl}-pyridin-3-yl)-naphthalen-1-yl]-urea;

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1-(5-tert-Butyl-2-methoxy-phenyl)-3-(4-{6-[(2-methylsulfanyl-ethylamino)-methyl]-pyridin-3-yl}-naphthalen-1-yl)-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

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1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2,6-dimethyl-morpholin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-(4-{6-[(2-piperazin-1-yl-ethylamino)-methyl]-pyridin-3-yl}-naphthalen-1-yl)-urea;

5 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(4-pyrimidin-2-yl-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(4-pyridin-2-yl-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

10 1-(5-tert-Butyl-2-methoxy-phenyl)-3-(4-{6-[4-(3-methoxy-phenyl)-piperazin-1-ylmethyl]-pyridin-3-yl}-naphthalen-1-yl)-urea;

15 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(morpholine-4-carbonyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2-thia-5-aza-bicyclo[2.2.1]hept-5-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

20 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(5-morpholin-4-ylmethyl-pyrazin-2-yl)-naphthalen-1-yl]-urea;

1-(6-tert-Butyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

25 1-(3-Amino-5-tert-butyl-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

30 N-(5-{4-[3-(5-tert-Butyl-2-methoxy-phenyl)-ureido]-naphthalen-1-yl}-pyridin-2-yl)-acetamide;

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-N-methyl-acetamide;

35 N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-2,2,2-trifluoro-acetamide;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(pyridin-3-yloxy)-pyridin-3-yl]-naphthalen-1-yl}-urea;

40 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(pyridin-3-ylamino)-pyridin-3-yl]-naphthalen-1-yl}-urea;

45 [4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-carbamic acid 3-tert-butyl-phenyl ester and



N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-methanesulfonamide or

the pharmaceutically acceptable derivatives thereof.

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10. A method of treating a cytokine mediated disease or condition chosen from: acute and chronic inflammation in the lung caused by inhalation of smoke, endometriosis, Behcet's disease, uveitis, ankylosing spondylitis, pancreatitis, cancer, Lyme disease, restenosis following percutaneous transluminal coronary angioplasty, traumatic arthritis, sepsis, chronic obstructive pulmonary disease and congestive heart failure, said method comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound chosen from:

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1-(3-Methyl-naphthalen-2-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

20 N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-acetamide;

1-[5-tert-Butyl-3-(2,3-dihydroxy-propyl)-2-hydroxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

25 1-(2,3-Dimethyl-1H-indol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-{5-tert-Butyl-2-methyl-3-[3-(tetrahydro-pyran-2-yloxy)-prop-1-ynyl]-phenyl}-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

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1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-(2,2-Dimethyl-propionyl)-2-methyl-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

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1-[5-tert-Butyl-3-(3-hydroxy-prop-1-ynyl)-2-methyl-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

40 1-[5-tert-Butyl-2-(3-hydroxy-prop-1-ynyl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-3-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

5 1-[5-tert-Butyl-3-(2,3-dihydroxy-propyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butoxy-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

10 1-[5-(1-Cyano-cyclopropyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[5-tert-Butyl-3-(2-diethylamino-ethyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

15 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-[1,3]dioxolan-2-yl-pyridin-3-yl)-naphthalen-1-yl]-urea;

20 1-(5-tert-Butyl-2-pyrrolidin-1-yl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-dimethylamino-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

25 1-(5-tert-Butyl-2-propoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-hydroxymethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

30 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2,6-dimethyl-morpholin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

35 1-(5-Cyclohexyl-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(2,4-Dimethoxy-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

40 1-(5-tert-Butyl-2-methoxy-3-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(3-Amino-5-tert-butyl-2-methoxy-phenyl)-3-[4-(6-methyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

45 N-Acetyl-N-(5-tert-butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-

naphthalen-1-yl]-ureido}-phenyl)-acetamide;

1-(6-tert-Butyl-4-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

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1-(5-tert-Butyl-2-ethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

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1-(5-tert-Butyl-2-isopropoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-imidazol-1-yl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

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1-(5-tert-Butyl-3-ethylamino-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-bis(methanesulfon)amide;

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1-[5-tert-Butyl-2-(1-methyl-1H-pyrazol-4-yl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

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1-(2-Methanesulfinyl-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[4-(6-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-pyridin-3-yl)-naphthalen-1-yl]-3-(5-tert-butyl-2-methoxy-phenyl)-urea;

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N-[1-(5-{4-[3-(5-tert-Butyl-2-methoxy-phenyl)-ureido]-naphthalen-1-yl}-pyridin-2-ylmethyl)-pyrrolidin-3-yl]-acetamide;

1-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

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N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-propionamide;

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1-(5-tert-Butyl-2-methyl-benzooxazol-7-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(3-trifluoromethanesulfonyl-phenyl)-urea;

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N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-isobutyramide;

2-(4-tert-Butyl-2-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenoxy)-acetamide;

5 1-(5-tert-Butyl-2-oxo-2,3-dihydro-benzooxazol-7-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-3-cyano-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

10 1-(5-tert-Butyl-benzooxazol-7-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

15 N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-benzenesulfonamide;

Ethanesulfonic acid (5-tert-butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-amide;

20 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(2-morpholin-4-ylmethyl-pyrimidin-5-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methylsulfanyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

25 1-(5-tert-Butyl-2-methoxy-pyridin-3-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

30 2,2,2-Trifluoro-ethanesulfonic acid (5-tert-butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-amide;

N-(5-{4-[3-(5-tert-Butyl-2-methyl-phenyl)-ureido]-naphthalen-1-yl}-pyrazin-2-yl)-methanesulfonamide;

35 1-[4-(6-{[Bis-(2-cyano-ethyl)-amino]-methyl}-pyridin-3-yl)-naphthalen-1-yl]-3-(5-tert-butyl-2-methoxy-phenyl)-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

40 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-thiomorpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

45 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2,6-dimethyl-piperidin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(1-oxo-tetrahydro-thiopyran-4-ylamino)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(tetrahydro-pyran-4-ylamino)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-[[2-(cyano-ethyl)-(tetrahydro-furan-2-ylmethyl)-amino]-methyl]-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2-methoxymethyl-morpholin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2-methyl-3-oxo-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-{4-[3-(5-tert-Butyl-2-methoxy-phenyl)-ureido]-naphthalen-1-yl}-pyridin-2-ylmethyl)-piperidine-3-carboxylic acid amide;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(1-oxo-1,4-thiomorpholin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-3-[4-(6-morpholin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(3-oxo-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-(4-{6-[(tetrahydro-furan-3-ylamino)-methyl]-pyridin-3-yl}-naphthalen-1-yl)-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-[[2-(cyano-ethyl)-pyridin-3-ylmethyl-amino]-methyl]-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2,6-dimethyl-morpholin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-(4-{6-[4-(3-methoxy-phenyl)-piperazin-1-ylmethyl]-pyridin-3-yl}-naphthalen-1-yl)-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(morpholine-4-carbonyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(5-morpholin-4-ylmethyl-pyrazin-2-yl)-

naphthalen-1-yl]-urea;

1-(6-tert-Butyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(3-Amino-5-tert-butyl-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

N-(5-{4-[3-(5-tert-Butyl-2-methoxy-phenyl)-ureido]-naphthalen-1-yl}-pyridin-2-yl)-acetamide;

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-N-methyl-acetamide;

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-2,2,2-trifluoro-acetamide;

1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(pyridin-3-yloxy)-pyridin-3-yl]-naphthalen-1-yl}-urea;

[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-carbamic acid 3-tert-butyl-phenyl ester and

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-methanesulfonamide and

or the pharmaceutically acceptable derivatives thereof.

11. A method of treating a cytokine mediated disease or condition chosen from: acute and chronic inflammation in the lung caused by inhalation of smoke, endometriosis, Behcet's disease, uveitis, ankylosing spondylitis, pancreatitis, cancer, Lyme disease, restenosis following percutaneous transluminal coronary angioplasty, traumatic arthritis, sepsis, chronic obstructive pulmonary disease and congestive heart failure, said method comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound chosen from::

1-(5-tert-Butyl-2-methylsulfanyl-pyridin-3-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-chloro-pyridin-3-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-

naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methylamino-pyridin-3-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

5 N-(5-tert-Butyl-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-2-oxo-2H-pyridin-1-yl)-methanesulfonamide;

10 5-tert-Butyl-7-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-benzooxazole-2-carboxylic acid amide;

2-(5-tert-Butyl-7-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-benzooxazol-2-yl)-acetamide;

15 5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-benzamide;

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-methanesulfonamide;

20 1-(3-Amino-5-tert-butyl-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea and

25 1-[5-tert-Butyl-3-(2,3-dihydroxy-propyl)-2-hydroxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea  
or

the pharmaceutically acceptable derivatives thereof.

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12. The method according to claims 1, 9, 10 or 11 wherein the cytokine mediated disease is chosen from sepsis, chronic obstructive pulmonary disease and congestive heart failure.

35 13. The method according to claims 1, 9, 10 or 11 wherein the cytokine mediated disease is chosen from chronic obstructive pulmonary disease and congestive heart failure.

14. The method according to claims 1, 9, 10 or 11 wherein the disease is chosen from acute and chronic inflammation in the lung caused by inhalation of smoke, endometriosis, Behcet's disease, uveitis, ankylosing spondylitis, pancreatitis, Lyme disease and cancer.

- 5 15. The method according to claim 1, 9, 10 or 11 wherein the disease is cancer and the treatment is done in conjunction with genotoxic therapy.